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ARMED FORCES EPIDEMIOLOGICAL BOARD

FALL MEETING

SEPTEMBER 21, 2004

OPEN SESSION

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DR. KILPATRICK: As the designated federal official for the Armed Forces Epidemiological Board of the Federal Advisory Committee to the Secretary of Defense, which serves as a continuing scientific advisory body to the Assistance Secretary of Defense for Health Affairs and the Surgeon's General of the military departments, I hearby call the fall 2004 meeting to order.

Colonel Turner, please accept my appreciation for your willingness to host this meeting, for arranging a tour of the Air Force Basic Military Training Center tomorrow. Your staff, in particular Major Tom Cheetom and Lieutenant Coolidge have provided outstanding support for the AFEB. It is certainly my pleasure to be here and participate in the ongoings, not only with this group but with this city. Thank you.

DR. OSTROFF: Thanks very much. I also would like to echo those thanks. If memory serves me correctly, the very first meeting that I attended as a member of the AFEB was actually here in San Antonio a number of years ago. I think there are probably still a couple of board members who were here back at that last meeting, which was, I imagine, four or five years ago. At that meeting we spent most of our time at Fort Sam Houston, and it was really a terrific visit. And it's also nice to come back to San Antonio. And so I would also like to thank Colonel Turner, who is the commander of the

59th Aeromedical Dental Group Command at Lackland Basic Military Training Center for hosting this particular meeting.

Okay. We have one distinguished guest with us this morning, Dr. Doug Wear, from the Armed Forces Institute of Pathology. If you could introduce yourself and maybe make a comment or two about your current position.

DR. WEAR: Well, thank you. I'm from the Armed Forces Institute of Pathology. I am representing my boss, Dr. Florabel Mullick, a distinguished scientist SCS4. At the institute we are heavily involved with the protection and identification of the folks that fall in Iraqi Freedom. We have the Dover Air Force work going. We are working very hard with the identification of the leishmaniasis diseases in our returning troops. We are very interested in supporting this Board and appreciate very much the honor of being here.

DR. OSTROFF: Thanks very much. For a number of years I was also a member of the Scientific Advisory Board at the AFIP. So please give my regards to Dr. Mullick.

I am going to turn the microphone over to Colonel Gibson for some administrative remarks.

COLONEL GIBSON: Great. I want to echo again the thanks to Colonel Turner and his staff, in particular, Tom Cheetom and Lieutenant Coolidge. We were on the phone with them time and time again trying to make these final arrangements, and they've been nothing but helpful during the

whole process. So thank you very much.

The next Board meeting will be on the 30th of November and the 1st of December. It'll be at the Island Club in Coronado in San Diego. A few of you on the Board were with us when we went there last time. That, I think, was two years ago. A tentative agenda includes a tour of the hospital ship Mercy and several important presentations. Potentially presentations on mental health among deployed troops, occupational health, and health promotion.

This meeting, the refreshments will be available both in the morning and afternoon. For this afternoon's session, we'll have these little lunches to -- or little -- after we have our working lunch today, we'll have these little pass-out lunches that you'll take for your break in the afternoon at -- because we're going to Brooks Air Force Base for the second -- for the closed session.

The working lunch today will be for the Board members and the preventative medicine officers and speakers. There's a number of restaurants. As you know, this is San Antonio, there's restaurants everywhere. Plenty of restaurants for the rest of you who are attending the meeting. As I said, following lunch, there'll be a bus outside the front of the hotel that we'll get on and go down to Brooks Air Force Base for a -- the closed session, question to the Board on the Active Denial System.

For those of you who have the appropriate clearances -- for the Board members, we took care of that for you. We got your clearances into the folks at Brooks for this meeting. And for the rest of you, you need to send your stuff through. We have a short list -- we'll have a list -- a final list of those who have -- whose clearances went through who can attend the afternoon session.

Tomorrow morning we'll be touring Lackland Air Force Base, the Air Force Basic Military Training Center. We'll have a quick breakfast here at about 7:00 and then get on a bus or buses and go down to Lackland, finish up there, have a tour of the basic training center, the clinic, et cetera, and lunch with the recruits in the dining hall.

Rest rooms are located outside the -- just outside the door here. And if you need a telephone, fax, or any type of message support, speak to Ms. Bralley back here. You want to turn your cell phones off, if you would please, at this point in the meeting.

Meeting transcripts will be up on the Web -- on our Web site in the next few weeks. This is a transcripted meeting. So ensure that you use your microphones during the process so we can capture the information. And there are really no final agendas.

I wanted to thank Severine for her hard work. We have 5.25 CEU credits, which isn't bad considering we have

a closed session and half a day doing the tour. So you have to fill out -- in addition to the registration outside, if you put your name on the other forms and pick up the -- pick up these, you can get the CEU credits.

Tonight we're going to meet at the hotel lobby at 6:45 for the -- for dinner. All of you are invited to attend, but we do need to get the names of -- or numbers of the folks. Tonight we're at Zuni's Grill. We have a Riverwalk cruise, a cocktail cruise on the Riverwalk, and we'll go from here to that at 6:45. After the cruise, then we'll do the dinner at Zuni's Grill down on the Riverwalk. And I think that's it.

DR. OSTROFF: Terrific organization. We didn't do the cruise the last time. So you one-upped me.

Before we get started with the rest of the program, since we do, as has been the case the last couple of meetings, have some new members. What I would like to start by doing, if we could, is going around the table and have people introduce themselves. That not only allows our new members to know who we are but also we can make sure we know who is here. So why don't we start over here on the far -- my far right.

(ALL ATTENDEES INTRODUCED THEMSELVES)

DR. OSTROFF: Thanks very much. I would like to get our program started. Colonel Turner is going to make a

few comments to open the meeting.

COLONEL TURNER: Good morning. Welcome to San Antonio. It sounds like you have quite a fun time planned. So after you go eat tonight, I would suggest you go to Howl at the Moon, and be sure to tell them it's your first time there.

Again, we're thrilled to have you here. We're very honored to have everyone here. It's going to be a great time, and this is such an impressive group of people with such a big impact on folks. It's great to see some old friends. I see Dr. Cox. Every time I see Dr. Cox, he's cut his hair shorter, while mine seems to be happy to go away on its own.

But I think this is a very exciting time to be in this very prospective thing. So such a great interagency, international, transformational group. Those that got all my 495 words in one sentence for that time, so I think I might qualify as a belt weight by now. But certainly the National Defense University Study of the globalized health industry last year certainly pointed out that we're on the cusp of not one but two great transformations in medicine.

You know, the first great change in medicine was microbes and the -- basically the transition to antibiotics as a therapy. But now we're fortunate enough to actually sit on the cusp of two great changes in medicine. The first one proteomics and genomics as far as a treatment to

specifically get that silver bullet, and what an amazing thing that is. But, to me, even more important is we are on the cusp of practicing -- going from practicing one patient at a time to practicing entire communities at a time. Technology now allows us to look at entire populations and how they act through an electronic medical record or through a number of other tools. And just as the Wright brothers first, you know, got aloft, you know, people could not foresee, except for some people -- except for some, what great impact this would have over the next few years. So certainly as we are able to develop electronic medical records and medical surveillance, the ability to make that giant paradigm shift with medicine, which is always focus on one patient at a time primarily, we now could practice medicine thousands -- entire communities at a time. And I think you guys are poised right on the cusp of such an incredible powerful time and an incredibly powerful way to make a difference.

Again, we're very, very honored and pleased to have you, look forward to seeing you over at Wilford Hall, and we'll give you a number for our favorite bail bondsman because this looks like a wild group. Again, thank you very, very much for coming to San Antone, and we look forward to seeing you.

DR. OSTROFF: We have a small token of appreciation. The plaque, which we had a little bit of

dyslexia here. We'll have to get that fixed, because it says it's to Colonel Truner instead of Colonel Turner, who established the 59th Aeromedical Dental Group. And this is presented to you. And then we also have (inaudible) coins.

COLONEL TURNER: Thank you very much.

(APPLAUSE)

DR. OSTROFF: Thanks. I would remiss if I didn't mention that we do have one Board member who was planning to be here but because of a health problem was unable to attend, and that's Dr. Haywood. And so we all hope that he's doing well, and we look forward to him being here at future meetings.

So with that, why don't we get started with the program. We have several questions that have been brought before the Board. The first question is under Tab 2, and it has to do with the programs for research on antimicrobial resistance issues and antimicrobial development. And we have a series of speakers this morning to both present the question and put it into some context.

The first of our speakers, who I believe, yes, is here, is a longtime friend of the Board, Colonel Bob Defraites, who is the director of the Proponents for Preventive Medicine, Office of the Army Surgeon General, and he is going to present the question to us.

Welcome.

COLONEL DEFRAITES: Hi. Good morning. And, Dr. Ostroff, it's a great pleasure and honor for me to be here to present this question to the Board. On behalf of our -- I guess, the 40th Surgeon General of the Army, Lieutenant General James B. Peake, who retired as of July -- but before he did, he had one last act to ask the Board: To ponder the question about the DoD's role in discovery and development of antimicrobial drugs.

I would like to say that we -- General Peake is the former Surgeon General, and also he's the only one we have. General Kiley -- Major General Kiley has been nominated to succeed him. His nomination has not yet been confirmed by the Senate, but we expect that to happen in -- over the next couple of weeks. General Kiley is the acting commander of -- commanding general of our U.S. Army medical command, and he is the nominee to be the 41st Surgeon General of the Army.

This morning I would like to present this question. And, again, it's going to be one of a series of briefs, and I'll just try to frame the question in terms of the DoD's role and then in the national role.

Next slide, please.

I just -- this slide just covers just a brief statement of the problem. And essentially there are two issues here: First of all, it's an interesting convergence of circumstances on three points. First of all, well -- well

recognized high levels of antibiotic resistance among very clinically important pathogens. Secondly, is what's termed as an uneven supply of new or novel antibiotics to counter these pathogens.

In general, my discussion, and I think General Peake's question, dealt mainly with bacteria or the talking about -- when we talk about antimicrobial resistance, we're focused mostly on bacteria. I think you'll hear some of the speakers talk about perhaps antivirals and antiparasitic agents in terms of some of the focus. But the main focus of the question is on bacteria. So antibacterial drugs have certainly been in uneven supply, and there are a few new drugs in the pipeline.

And, thirdly, is a dramatic reduction in industry in terms of the number of pharmaceutical companies that are engaged in new drug discovery and development. One of my major sources for your remarks this morning is this article -- very recent article by Dr. Wenzel in the New England Journal of Medicine from last month. And so a lot of the material that I'll be talking about this morning is focused on his great discussion in this paper.

Next slide, please.

Just a brief recap of antimicrobial resistance. And, again, I'm not going to read this slide, but, essentially, from the beginning of the antibiotic era in the

'20s to the '40s and '50s, we saw the emergence of beta-lactamase producing bacteria that were resistant to penicillin, methicillin-resistant staph aureus in the '70s and '80s, and then today the statement of the problem, which, I guess -- I don't want to go into too much detail, but essentially strep pneumonia isolates in the community of being resistant to penicillin, staph aureus isolates in the hospital of being methicillin resistant -- that's easy for me to say -- about half of them in hospital-acquired patients are methicillin resistant, and also an emerging problem of enterococci that are resistant to the vancomycin, just to give some examples.

Next slide, please.

Now, in the second point, decreased deployment of new antibiotics, again, this sort of recaps the history of development of antimicrobials from the development early on of the classes of drugs that you see listed for the '30s and the '40s, the penicillin sulfonamides, aminoglycosides, chloramphenicol; in the '50s and '60s, development of other -- these other drugs; and in the '70s and the '90s, I put question marks there, because there seems to be a gap with a lessening in development and discovery and release of new drugs. And then in this decade the -- these last two, the cyclic lipopeptides and the oxazolidinones. Easy, again, for me to say. I tried practicing that, but it doesn't work early

morning before two cups of coffee.

Next slide, please.

Now, the risky business -- the -- on the business side. Again, it's -- one way to discuss this is in terms of -- from a business perspective in terms of deciding where you want to put your risk in terms of development and investment of stockholder interest. There is a term called risk-adjusted net present value, and that essentially tells you what your return in future millions of dollars, after adjustment for investment and lost income. This doesn't include the risk of failure. In other words, drugs that don't make it through the pipeline. The time of such is -- you know, that's one of the opportunity costs, time and other direct and indirect costs, focussing, for example, a research program in one direction that doesn't bear fruit.

However, if you look at -- at relative net present value -- or risk-adjusted net present values of different types of drugs, if you're in the drug business, which you can expect to return, for antibiotics you can expect to -- over the life of an antibiotic and assumes about a ten year existence of a patent before the patent expires, then you can get about $100 million for most antibiotics. And, again, my source for this information was Dr. Wenzel's article. So about $100 million for antibiotics as compared to for cancer therapies about $300 million, for neurological drugs about

$720 million, and for musculoskeletal drugs, nonsteriodal anti-inflammatories, and other musculoskeletal drugs, about $1150 million. But you can see, if you had to -- had to pick and choose among classes of drugs to put your -- to devote your resource -- research effort, that antibiotics really don't give you a big return on your investment dollar. And as result of that -- or, you know, and other reasons, too, but since the mid-1980s fewer of the large pharmaceutical firms are investing in anti-infective drugs as a major product line.

Next slide, please.

This is a quote from the CBS news story on "60 Minutes" in May. Now, at that time, "60 Minutes" I think might have had a better reputation than it does today. But at least at that time, they had -- they were discussing pharmaceutical -- the problem with antibiotic resistance. And here's a quote from that program -- and, again, this program and other -- other issues at the time were really what stimulated the question to the Board. But here is just a quote from Dr. Schaffner from Vanderbilt saying, (as read) "In the year 2002, about 400 new agents were licensed by the FDA, and really no genuinely" -- in other words, new classes or novel classes of antibiotics among them. And that's a very striking thing in this day and age.

Next slide, please.

And so the Army question to the Board

essentially is the following -- you'll here from Dr. Vaughn -- Colonel Vaughn later on this morning. He'll describe the military infectious disease research program in a portfolio of research efforts we have ongoing, and really you'll see that it doesn't really include any effort to develop new antibacterial, antimicrobial agents for multi drug-resistant organisms. You'll also hear from some of our speakers this morning that we do have a military-specific problem with multi drug-resistant organisms. You'll hear from some of our speakers about that.

So General Peake in the Army asked the Board to review the issue of emerging antibiotic resistant microbes. And then to finally recommend a role -- or the role -- proper role of the military medical research community in the development of new or novel antibiotics that treat infections caused by these multi drug-resistant organisms.

With that, I'll end my -- those of -- end my prepared remarks, and I'll be glad to answer some questions.

DR. OSTROFF: Thanks very much.

Dr. Poland.

DR. POLAND: Just a nuance of word there, is it that -- is this an active or passive problem? That is, does the research portfolio actively prevent --

COLONEL DEFRAITES: No.

DR. POLAND: -- the problem?

COLONEL DEFRAITES: It just -- it does not -- well, I used the word "exclude," but you'll just see it omits --

DR. POLAND: Okay.

COLONEL DEFRAITES: -- I guess that would be -- it just doesn't include --

DR. POLAND: Okay.

COLONEL DEFRAITES: -- exclude -- it just -- it does not include -- but it's not -- well, I mean, there is a -- there is a purposeful, I think, winnowing of research efforts, and, again, weighing, you know, military relevance. And maybe Colonel Vaughn can go into some of the rationale behind the existing portfolio. But there isn't -- there hasn't been, I think, an active exclusion of this as an issue.

DR. OSTROFF: Other comments or questions?

My only comment would be that you should have included the net present value for the erectile dysfunction drugs, based on how heavily they're advertised. I wonder where they come out on the scale as well.

COLONEL DEFRAITES: Yeah, it wasn't mentioned in there.

DR. OSTROFF: Thanks very much. Why don't we move on to our next presentation. And we have Commander Clara Whitt, who is from DoD-GEIS. She is the deputy director for antimicrobial resistant, zoonotic and

vectorborne disease surveillance. So she's quite a busy person, and she's going to provide some information on some of the challenges related to antimicrobial resistance in the Department of Defense. Thanks.

COMMANDER WHITT: Good morning. Thank you for having me here today.

DR. OSTROFF: And your slides are also in cab two just behind the ones from Colonel DeFraites.

COMMANDER WHITT: Thank you. As a way of facilitating the Board's deliberation this morning of General Peake's memorandum, we've organized a series of presentations that overview antimicrobial resistance as addressed by the Department of Defense.

Next.

But instead of just doing a series of passive presentations -- or passive on your part; it's pretty intense for us -- with your permission, we would like you to use the presentations in the form of GAP analysis type of exercise. The presentation should show us what the DoD is currently doing to address antimicrobial resistance and help -- help the Board identify areas where the department might consider strengthening its efforts.

Okay. Next.

In building the concept for this exercise, I turn to the 1997 Institute of Medicine work reports. And I'll

leave this on the table here if people want to refer to it later. And this report succinctly states that antimicrobial resistance is not a simple straightforward problem with a single and all-encompassing solution. In fact, the report said that everything that we do to expose bacteria to antibiotics gives them the opportunity to develop resistance, and we need to keep that in mind, if we truly want to combat -- if we truly want to combat antimicrobial resistance as a public health and as a clinical threat. The IOM stated that we need to focus on where we can do the most good with respect to antimicrobial resistance, because it can be -- if we approach the problem indiscriminately or without forethought, we can find ourselves in a no-win situation with respect to our (inaudible) against these types of infections. Therefore, we need to focus on controlling or slowing the emergence of resistance, and we need to prevent its spread between both bacteria and between people.

Next.

After the IOM workshop, a U.S. interagency task force was constituted to develop a federal action plan for combatting antimicrobial resistance within the country. That task force is made up of 11 federal agencies, including the Department of Defense. And by January of 2001, the task force developed this national plan. And, again, I'll leave this up here on the table. But you can access copies of this through

the CDC Web site. Also, this plan basically presents a blueprint for the federal government's approach to the antimicrobial resistance problem.

Also, in your packages, you'll find a copy of the annual report the DoD submits every year to the task force in accordance with the plan. And that document lists the focus areas and action items under the national plan, and -- next. And here I've got that circled in red. And it catalogs the DoD antimicrobial resistance projects or activities that are currently going on for the year of the report. Now, it may be that in the report not everything that the Department of Defense does with respect to resistance is listed in the report. For example, the report does not include the clinical work done by individual health care facilities. This submission is not -- the report is not meant to delve into that type of fine detail. But for our purposes today, we can get an indication of that sort of detail really through the presentations that will follow this morning.

Next.

Organizationally, the federal action plan divides the U.S. approach into four main focus areas and 84 action items. And these should be undertaken by the country as a whole and by each of the constituents of the country or each of the components of the federal government, if we wish to have a comprehensive national program for

combatting resistance. In reality, as all of our resources are not infinite, 13 of the 84 action items in the plan are designated as priority for implementation. The four focus areas are surveillance, as shown here. And surveillance has 20 action items, two of which have been designated as priorities. And by surveillance, we basically mean the monitoring of resistance by using susceptibility testing and also the tracking of drug usage patterns.

Next.

The second focus area is prevention and control, with five priority activities. And its aim is to extend the useful life of antimicrobials through prudent use by both prescribers and consumers. It also calls for improving diagnostic testing practices so that we are not using antimicrobials where they'll do no good, and it calls for preventing the need for antimicrobials through improved infection control practices and the use of vaccines.

Next.

The third area is research. It has three priority areas that focus on the development, testing, and evaluation of new rapid diagnostics and novel therapeutics and interventions for preventing the emergence and spread of resistant pathogens.

Next.

And the fourth focus area is product

development, and it has two priority activities. And it calls for the development of new drugs, including innovative, target, and narrow-spectrum targeting -- an innovative target, and narrow-spectrum antibiotics, as well as point-of-care diagnostics, vaccines and other biologics, and anti-infective medical devices and disinfectants.

Next.

By using the action plan, we can get an appreciation of the breath of approaches called for in any successful fight against antimicrobial resistance within the United States and, of course, globally. Within the DoD, we know -- or at least we have to assume that we have resistant bacteria in our hospitals and our treatment facilities. Antimicrobial resistance is certainly in our communities and in our training centers. Antimicrobial resistance involves the DoD, as much as any other organization or population. In that respect, we're not unique, and we're certainly not immune. Thank you.

Next.

So as a framework for our GAP analysis, I've taken the action plan, and I've drafted a matrix that can be used to start inventorying our current DoD activities. You have a copy of the matrix in your packages. The first two columns categorize DoD activities into four focus areas and the relevant action items in the U.S. plan.

Next.

To ease the work of the Board, I've taken the liberty of shortening and paraphrasing the focus areas into more DoD relevant purposes. For example, for surveillance, its purpose is to define and update empiric and standard treatment guidelines, reassess our drug formularies, assure that the drug supply is appropriate for our needs, and identify any needs for implementing infection control measures, and monitor for the impact of any instituted interventions.

Next.

For prevention and control, research and product development, I've reformatted the purposes similarly, as you can see here, and in your papers -- in your packages.

Next.

I've done the same for the action items in the second column. But, again, you can refer back to the original national plan on the DoD submission if you prefer to really work with the original wording.

Next.

In the last four columns of the matrix, I've listed which I consider the generic players within DoD that have a role in dealing with antimicrobial resistance. That is, our treatment facilities, our MTF that services the DoD as a whole, and while not completely necessary for the purposes

of the Board today, I've included a column for OCONUS activities, overseas activities. That -- that sort of activity would include the DoD labs and other overseas assets. For example, it would include any overseas research conducted by (inaudible) on resistant (inaudible) or something like that.

Next.

The resulting matrix boxes on the right are there for you to list activities or projects identified as being conducted by any of the components within the DoD. And to start things off, I considered some of the activities that I know exist, because they are supported through our office, GEIS. These include both CONUS and OCONUS activities and are designated by a brief description of the activity, just as a notation that something within that box is being done. Finally, by listing an activity, I certainly made no assumptions about the activity's size, its effectiveness, or its breath, just the fact that it exists. The attributes of any given activity for this exercise, we can discuss that later if people are interested.

Next.

So as we hear the following presentations this morning and we learn more about the activities being done within the DoD on antimicrobial resistance, the Board can just record them on the appropriate squares on the matrix sheets.

And by the end of the exercise, the Board should have a matrix that shows the scope of the current DoD activities and where this work fits into the framework of the overall U.S. antimicrobial resistant action plan. And from there, you should also -- the Board should also be in a position to visualize where DoD's GAPs and possible future directions lie with respect to this topic. I certainly hope that this exercise serves as a useful starting point for the Board's deliberation on General Peake's questions and memorandum. Thank you very much.

DR. OSTROFF: Thank you very much. Let me open it up and ask if there are any questions or comments.

Dr. Herbold.

DR. HERBOLD: In the past 20 years or so when they were dealing with penicillin producing (inaudible) gonorrhea, the question was raised -- a policy question was raised about a military uniqueness. So I would presume that today the more important OCONUS issue for me is that's the exposure potential for military members to bring organisms -- to come in contact with organisms that are not in circulation today in the States. So as -- you mentioned the overseas labs, but my focus would be on the sentinel population of the military members that are OCONUS. And then -- and so is there anything going on as far as surveillance, culturing, isolation of organisms, wounds in military members that are outside the

United States?

COMMANDER WHITT: I'm most familiar with the projects and the works supported through my office. And the focus of those projects are mainly on surveillance and research in antimicrobial resistance on indigenous populations, on local populations, because we -- we all share bacteria, we're all potentially exposed, whether it's a tourist or whether it's a fighting member of the Force. And so there's a potential for exposure, and it's important that we know what our Force is being exposed to when it is overseas.

Now, with that being said, where we have the issues of drug-resistant bacterial infections in our fighting members, we -- certainly if the Army is in the middle of establishing an (inaudible) right now. We do look at these types of infections, looking to see where we can either prevent these infections or treat them optimally. I'm referring to the acinetobacter outbreak right now.

DR. HERBOLD: Right. I'm not talking about outbreaks and response. But do we have any systematic surveillance as we do for influenza drift? Do we have any systematic surveillance similar for bacterial pathogens that are coming through the established overseas medical treatment facilities that the military has that treat active duty and independent people?

COMMANDER WHITT: The -- you will hear later this afternoon -- or this morning a description of a program that we have as a cooperative agreement with Focus Technologies to do laboratory-based susceptibility tests monitoring. At the present time that is -- that program is limited to three facilities. And we're hoping to broaden that, but we're not there yet. So the long answer to your question is no, but there are -- there are some highlights that are focally happening.

DR. OSTROFF: The short answer is no. And I think that's the point, is that there isn't a systematic surveillance infrastructure in the DoD or, I think, in any of the services to collect these types of data probably in the way all of us would think would be most helpful. There is -- I think as Commander Whitt said, there is a lot of activity. And I don't know if any of the other Board members participated in reading what took place related to acinetobacter earlier in the summer. I was there talking about -- and this -- you know, precisely the way that this problem was identified.

DR. IRVING: Let me just point out real quickly that the Naval Health Research Center does do DoD GEIS sponsored surveillance for both Group A streptococcus and streptococcus pneumonia from military treatment facilities. They collect those and send on the isolates to the Naval

Health Research Center. We look at the antibiotic resistance pattern and have published on those two pathogens.

COLONEL GIBSON: And the Services can correct me -- this is Colonel Gibson -- correct me if I'm wrong, but as far as gonorrhea, STD, we move to basically the standard of care in the United States rather than -- doing the general diagnosis rather than culturing those things out and doing antimicrobial grams against them. So you bring a very important issue to the table Dr. Irving.

DR. OSTROFF: Dr. Gardner.

DR. GARDNER: I think -- just to introduce a distinction that I think sometimes is fuzzed quite a bit. The approach to infection by resistant organisms is a different problem than the prevalence of organisms that are resistant to bacteria. In the -- in preventing hospital-acquired infections by sensitive or resistant organisms, the emphasis is on the (inaudible) taught us, soap, water, and common sense are the best disinfectants. In the issue of the prevalence of organisms, you get -- it's our intention to focus on uses of antibiotics and how many tons of antibiotics we've -- according to the system -- including the large amount of antibiotics used in the agricultural field, which contribute to the prevalence from which some subset -- so I think that is a distinction.

What do you do about just reducing antibiotic

resistance in general? And then the second question, well, what about preventing infection in a (inaudible) setting? We're mostly concerned with the latter in this group, I think.

Just one last -- the world health organizations also have been working on this issue, and we'll stand (inaudible) effort, and that seems to me it's going to cover a lot of the issues that we're talking about here as well -- as well as the IOM. So there's plenty of attention being -- happening on this, and I guess our test is to figure out the military issues that are unique.

COMMANDER WHITT: If you look at the WHO strategic plan, it's written with the target audience of various nations of various economic and research capabilities. But if you look under the plan, it is the WHO strategy. It is very similar to the U.S. plans because the science drives what needs to be done to address the issue.

DR. OSTROFF: Dr. Brown.

DR. BROWN: Thank you. This Is Mark Brown. Question for the speaker: It seems to be -- when you're talking about the recommendations of this task force for how to minimize the development of antibiotic resistance, that there are two categories of recommendations. And one had to do with changing medical practices to, I guess, whatever prescription of antibiotics; and the second was the possibility of developing brand-new antibiotics that will

overcome resistance. But in terms of the first area for development -- for the prevention of development of resistance in the first place, you just briefly talked -- and Dr. Gardner mentioned it and you just briefly mentioned the issue of antibiotic resistant -- antibiotic use in agriculture, which is a big issue -- at least it had been in the past. And I was wondering if you could comment on what the consensus is today about the impact of agricultural use of antibiotics is on the overall problem of antibiotic resistance?

COMMANDER WHITT: There's no quick answer, other than to say there really is no general consensus on the impact of the agricultural use of antibiotics. There is certainly evidence to suggest that the indiscriminate use of antibiotics for growth promotion and the spread of resistant organisms from the animal sector into the environment or directly into the consumption chain affects -- are human -- human hosting resistant organisms. The Scandinavians certainly have done a lot of work in looking at the agricultural impact on resistance. The USDA, the FDA are also looking at a lot of what is -- actually is going on. But I think Dr. Powers may be able to answer that a little bit more definitively than I. But the last I heard was there's enough argument on both sides, the pros and the cons, for the use of microbials in animals, that I wouldn't want to say that

there's consensus.

DR. POWERS: Maybe I can help with some of those discussions. The Center for Preventionary Medicine last year put out a guidance about what we're going to do in terms of approvals of new antimicrobials going forward in animals because of this very issue. And at an advisory committee, we looked at some of the evidence regarding antimicrobial resistance spread from animals to humans. It clearly occurs. And last year at the interscience conference on antimicrobial agents in chemotherapy, some French investigators presented cases of urinary tract infections in women where the e. coli that they isolated had resistance to an antibiotic that is only used in animals. So that shows you that there is directly a link there. And then the CDC did some work that showed quinolone resistance that was being -- and campylobacter being spread from animals to humans.

What becomes impossible to determine, at least at the present time, is what is the percentage of resistance in humans that comes from animals. Although, my personal feeling is that's a moot point, because any amount is probably too much. And what we know about antibiotic resistance is once it gets rolling, it is much harder to stop at that point. So one of the things that Clara brought up is -- and that we don't have information on is the amount of antibiotics that are being used in either humans or animals.

What I learned last year doing this, is there are eight billion chickens in the United States. So if you think that usage of antibiotics makes an impact in humans, imagine what it does in terms of animal usage as well. So without knowing how much antibiotics actually get used in animals, which is numbers we don't have, it is impossible then to calculate what the impact could possibly be.

COMMANDER WHITT: That is the one good thing I've heard about avian influenza from this spring.

DR. OSTROFF: Any other questions or comments?

My only other comment would be, that when we think of agricultural use of antibiotics, the only strength in using an animal is because there's a lot that gets used in other settings, such as for plant growth promotion, et cetera. So there's antibiotics everywhere. That probably is outside the scope of this discussion since it's hard for the DoD to impact that type of use, but it is definitely worth thinking about.

Why don't we go on to our next presentation. We have Colonel Duane Hospenthal, who is from Brooke Army Medical Center. And he's going to speak to us about experience with antimicrobial resistance at BAMC. Welcome.

DR. HOSPENTHAL: Good morning. I was asked to give a snapshot of our medical center and our experiences with antimicrobial resistance, what we do, what we see, and some of

the research that we've done in the past.

Next slide.

Just as a couple brief introductory slides -- they're probably things that we probably all know anyway. I wanted to go over some of the recent patterns that we're seeing in some of the anecdotal reports that we hear. For the gram-positive cocci for staph aureus and enterococcus, certainly there is a documented increase in MRSA recovery in hospitals in this country, especially in ICUs. And this is well over
15 percent of our staph aureus at this point. More alarming are the reports of community acquired MRSA and what appears to be a more virulent strain of staph aureus in this community acquired MRSA. There is increasing VRE colonization infection. And even with the new drugs for VRE, such as linezolid, we are seeing resistance cropping up, and certainly vancomycin resistant staph aureus is slowly planing away.

Next slide.

On the gram-negative side, certainly the recent importation of MDRO and acinetobacter is being looked upon by many others. And one of the big problems being identified by the IDSA and others to include in our hospitals is increasing resistance in our MDRO drugs, our infections. And probably the best alarming marker I could find for that was really the resurrection of older toxic drugs that we are using to treat

some of these infections.

Next slide.

Well, at BAMC -- I was going to stress what we do at BAMC and what we see. This is what we do at BAMC: The microbiology lab tracks all our reportable agents. It's not clear to me how those are actually selected, but certainly there are the CDC reportable agents and then specific pathogens as they define them for resistance based on the (inaudible) that we use and the other tests that we do. Infection control then tracks colonization and infection with a select group of problem agents, which may or may not align with the microbiology agents, but these are mainly the ones that are suggested by the JCAHO, the CDC, and other agencies. And this includes your standard MRSA, (inaudible), VRE, and then this whole group that are called MDROs.

Next slide.

This basically is a summary of what the infection control collects at our hospital. And as you can see, we follow VRE, which isn't a big problem at BAMC. We follow MRSA. The numbers are somewhat inflated here in the MRSA. Since I moved to BAMC, we've done several studies of colonization, and so some of the graphs are various cultures. All of our results here are really by individual, by year, based on recovery of organizations. So they include colonization as well as infection. And as you can see, the

MDRO gram-negative rods really have only been tracked over the last year or two. The confusing column here, and the -- what will show up as an estimated 2004, is just a calculation based on this being the first eight months of the year, and what we expect for the overall should be at the end of the year for future reference.

Next slide.

So basically I was just going to go over our experience broken down into gram positives and gram negatives, talk a little bit about our gram positives and some of the research we're doing.

Next slide.

So first off, MRSA, that's nosocomial.

Next slide.

Our nosocomial rate at BAMC, we really do not see any alarming trends in the MRSA. Our rates are fairly low and do compare well with the NNIS. There are some blips. The axis really isn't very high, and this is what we've seen since the first quarter of 2000.

Next slide.

Community-acquired is certainly one of our bigger questions. Though it hasn't really been identified as an issue at BAMC.

Next slide.

Just a little background on the changing and

emerging epidemiology. Again, I apologize if you-all are well aware of all of this. Penicillin resistance was reported in the 1940s right after the introduction of penicillin. Methicillin resistance was reported in 1960 right after the introduction of methicillin. This is usually due to a unique penicillin binding protein change called a PBP two prime. In 1968, first U.S. outbreaks in hospitals and nosocomial (inaudible) were started out. And as I said up front, about

50 percent of these staph aureuses now in ICUs are MRSA, and at some centers this is 60, 70, and 80 percent anecdotally. Generally this is not an outpatient issue or has not been in the past.

Next slide.

More recently there's been many reports about community MRSA, and this has slowly developed over the last ten to 20 years. It has not rapidly come upon us. Except for the last several years, there seems to be, at least anecdotally, an increase in this problem. Certainly we've seen many cases in the pacific and Hawaii when I was there of community-acquired fluoroquinolosis on recurrent abscesses. Definitions are not exact at this point, and basically they're the same definitions in the reverse for nosocomial infections. Patients obtain their colonization or infection as outpatient over less than 48 hours in hospitalization. They have had -- not had hospitalization in the past year or renal dialysis

surgery, et cetera, et cetera, and there's no history of prior infection or colonization from a health care setting.

Next slide.

And if you follow the (inaudible), which I'm sure you all do, certainly reports have been coming in in the last couple of years -- actually probably for the last decade now on soft tissue infection in children, in athletes -- high school athletes, college athletes, county jails on the west coast, county jails and prisons in Texas, and Native Americans and other groups. Some of the more alarming reports have been several reports of sepsis, both fatal and nonfatal in children who apparently have no exposure to either the health care system or others with chronic health care exposure. And I think probably even more important is recent studies have increased what appears to be more virulence in these strains of pathogens.

Next slide.

There are several mec genes that encode for modified penicillin binding protein. The one that seems an associate of community-acquired MRSAs is the Type IV gene, and this gene is actually a smaller cluster than the other mec genes. There is certainly a lot of -- non -- not well proven postulations that the nosocomial strains of MRSA that carry lots of drug resistance and then these MRSAs that come in that are only susceptible to vancomycin, that they carry a large

component of genes for all these susceptibilities and with this they're a little less virulent and a little less fit. This is probably the opposite of what is probably going on with the community-acquired strains. These seem to carry only the MR -- the MRSA gene, and they don't really carry other antimicrobial resistance genes. So you see that they are susceptible to some of the other common inexpensive antibiotics, such as the trimethylenes and sulfamethoxazole and the clindamycins, occasionally the fluoroquinolones as well. But they also seem to carry virulence to the genes, more commonly to include the enterotoxin H genes and the Panton-Valentine leukocidin gene.

Next slide.

PVL, if you haven't kept up on this, is transmitted to the temperate phage. It is -- seems to be more and more common in the majority of the community-acquired MRSAs, and in our studies, it -- that seems to be in almost all of them that are causing disease. It is associated with severe skin and soft tissue infections, necrotizing pneumonia, and lyses leukocytes in vitro, and in animals you can show thermolysis. And also, not as well proven, but has been reported that this is a more fit bacteria than other staph aureus. It grows a little faster, it doubles a little faster, it does better on -- in microbiology situations.

Next slide.

What have we been doing? Well, we certainly have not identified a huge problem at BAMC, as I showed you our nosocomial data. But we have been doing some research both in Hawaii in inpatient and outpatient colonization studies and more recently at BAMC in some inpatient, outpatient colonization studies. What we are looking at in both these next two studies that I'll show you is how does colonization affect outcome and does it affect outcome.

The first study we did at BAMC started several years ago. And basically we screened patients in selective units. One medical ICU; one surgical ICU; one trauma ICU; and one general medicine ward; and one telemetry unit for colonization of MRSA (inaudible) on admission. We screened 500 -- or 758 patients -- well, we screened about 1,000 patients, but we have data, complete sets, for 758 patients. We followed these folks one year with electronic records and found that in our colonized patients, those colonized with MRSA certainly had a higher rate of developing infection down the road. Colonization rate really didn't seem much higher than what's been reported in the past. And so, even here, we do not really identify an issue at BAMC or in San Antonio. Define 17 to 25 MSSA colonization with swabbing and probably two and a half to 6 percent MRSA colonization swabbing is probably normal for studies in the last decade or two.

Next slide.

Probably more interesting for the military, though, perhaps not for a medical center, is our outpatient studies that we had started. This is the first of the series. We have complete data sets for 812 healthy human volunteers. These are combat medic trainees. These are folks who are coming from the more clustered subset from basic training around the country and then coming to Fort Sam Houston, actually, and so they do not have any clinical duties, they do not interact with the medical health care system, even though they are medical health care trainees. They stay at the AMEDD Center and School, and they really don't have any of the risk factors for MRSA. And this is what we found in those folks. On initial swabbing when they arrived at Fort Sam Houston, about 3 percent had MRSA colonization and about 28 percent had methicillin-sensitive colonization. We followed these folks up, got demographics and risk factors at eight to ten weeks. Prior to their first field experience, we reswabbed them. So this was an eight to ten week classroom experience for them, housed really not in the clustered basic training housing, but more in a college-style setting housing. So a little more space between, a little more privacy. And what we found here was that of the MRSA colonizing, even though it was a small number, 38 percent actually developed infection, skin and soft tissue. And this was much lower in the staph aureus colonization.

Next slide.

What we also found in that study was -- what -- what you might expect, which is if you were colonized with MSSA, you had a much lower risk of picking up an MRSA, because the niche was already filled, because if you were uncolonized, you had a higher rate of picking up MRSA during this period. The overall trend, though, was that people became less colonized as that went through this training period. But of those that had MRSA, community-acquired, two-thirds of them had PVL genes. Of them that developed infections, to include the ones that had colonization with MSSA or were not colonized, those that developed infections who had recovered organisms had recovered MRSA, and all of those had PVL genes. And this included one patient who chose not to participate, who came in bacteremic with an MRSA with PVL genes, which actually by RFLP matched the most predominant strain that we had seen as well.

Next slide.

Vancomycin-resistant enterococcus.

Next slide.

Really has never been a problem at BAMC. We do no solid organ or stem cell transplantation in our facility, and thus this seems to be much less common. We are a Level 1 trauma center, so we do have some long-term trauma patients, but even with that, with our infection control policies, we

don't see much of VRE.

Next slide.

And this seems to jump around a pit, but if you look at the axis, we're really talking only zero to four infections or colonizations per 100,000 bed days.

Next slide.

I threw this in just because there was a request for me to track antibiotic usage as well, and I did track some of the more interesting antibiotics. This does look like it's going up. But, again, it kind of goes up from the date of introduction when it was added to the formulary and how it's become a more convenient tool to treat some of our MRSA, more than we use in our VRE patients, which are very few.

Next slide.

MDROs is probably the biggest problem.

Next slide.

It's not even really clear all the time what an MDRO is. These are bacteria resistant -- by the CDC definitions, these are bacteria that are resistant to at least one class of antibiotics, antimicrobials, and susceptible to two or less of the commonly used antimicrobials. We find this definition somewhat vague at our hospital, and we've looked it up several ways. It's very difficult to work with. I'm not sure whether I lump together

beta-lactamase-like products with all the aminoglycosides in one group or whether I can break them into two classes, et cetera. And also the MDRO, even though this fits for VRE and MRSA, it really is only used in tracking purposes to talk about gram-negative rods, which is how I use it in the rest of the talk.

Next slide.

So the definitions are imperfect. They're really based on what antimicrobials you test. There are certainly suggestions from the NCC what you shouldn't test for which particular bacteria for where you got that bacteria from, sterile site, nonsterile site, blood, urine, et cetera. But it really comes down to me and the chief of microbiology sitting down and seeing what Vitek cards really match our practice, not the things that we see. There's not one card that fits all institutions. And if you don't use Vitek, it's even probably more problematic if you're using Kirby Bowers or other methods.

The other problem I can find with this is the reporting does not really identify how resistant the bacteria are. And this was a problem when we first started looking at our acinetobacter problem, because even though the acinetobacter were very resistant coming out of Iraq, several of them did not fit the MDRO definition, and thus they were not tracked, because they still had (inaudible) and

(inaudible) and some of them had (inaudible), and so they did not fit that category. And it really doesn't tell me how many bacteria have one class left, you know, which bacterias, which pseudomonas in the ICU is only susceptible to (inaudible) and no other antibiotics.

Next slide.

So this is what we're talking about. Again, I don't have great data. There is data from (inaudible), but infection control does not track this until recently.

Next slide.

Just a little bit about our acinetobacter series.

Next slide.

You know, is this the canary in the coal mine; is this waking us up to there is a lot of resistance out there and it's getting worse? This has become a problem and been identified with the soldiers coming back from Iraq, which certainly has been problem with nosocomial infections for quite a while. It is commonly found, if you screen and swab people working in ICUs, if you swab tracheostomy sites. The NNIS data identifies it currently at about .6 percent of hospital-acquired infections and 3 percent of hospital-acquired pneumonias. Historical note, it is the most gram-negative contaminating traumatic injuries in the Vietnam conflict as well as in the Iraqi conflict.

Next slide.

So it's been there before. This was first brought to our attention when colonization wound infections were noted on the -- on the navy ship Comfort -- the hospital ship Comfort at the onset of OIF. And when that was actually studied, about a third of the wound cultures and about a quarter of the folks that are wounded in action were found to either be colonized or, even more commonly, infected with this organism.

Next slide.

This data is probably imperfect, and I can be corrected after my talk on this. But in the first of the meetings on acinetobacter with data up to June of 2004, there was about 30 -- 350 colonizations documented, with about 200 infections.

Next slide.

So back to BAMC and what's been going on in our place. Well, this is our infection control charting acinetobacter, and, as you can see, our nosocomial rates have been fairly steady, even throughout this even with the Iraqi returning soldiers. What has changed is what's being called community-acquired infections. And for those of you who know infection control, these can be acquired anywhere. They're just not acquired at our hospital.

Next slide.

When we actually looked at this for the acinetobacter conference that met a month or two ago, this is the early data that we had up until May of '04. And what we found is that active duty service personnel admitted with injuries, acinetobacter had not been a problem in the year prior to the Iraqi conflict. And in this short period thereafter, we had 46 people with positive cultures.

Next slide.

So cultures of those, about two thirds were actually thought to be infection and a third were thought to be colonization.

Next slide.

Of those who -- of those 56, about 86 percent of them actually had OIF exposure, but several of them did not. Two of which, though, looked like they were actually cross infections in our ICUs in our burn center. And this is certainly the issue that's being raised with all this acinetobacter returning from the gulf, is will we spread this into our ICUs and will this become a permanent fixture in our ICUs for the next decade or so.

Next slide.

Just a note from that same white paper or provisional white paper from the meeting, most of these remain sensitive to imipenem/cilastatin. A small population of them are still sensitive to (inaudible). About a quarter are

sensitive to amikacin thus far. But two have been found to be resistant to all the tested antimicrobials, though not at BAMC. Those were other centers' patients.

Next slide.

At that past meeting, there was certainly mention of tracking the carbapenem usage, and so I put that together for BAMC. Certainly there is increased carbapenem usage in out last -- last year. And our estimate is -- estimate is that it's going to increase quite a bit by the end of this year. But as you can see, this bar was going up well before the Iraqi conflict and does in some ways, I believe, reflect our more resistant gram-negative rods. Carbapenems at BAMC, as in many facilities, are held out as the last drug class to be saved for multiple drug resistant pseudomonas and ESPL organisms in the ICUs.

Next slide.

Other gram-negative rods.

Next slide.

Certainly the database for the other gram-negative rods is much more problematic. Infection control tracking only recently started. We do have a microbiology database. Certainly all that data is there. It's probably all there for the last 20 years from our Vitek machine and it's correlated and put into big sheets and files, but it's not readily available to me. And, again, it's not

readily available to me how resistant these gram-negative rods are. And certainly anecdotally, probably every month on the consult service, there's somebody who is running out of drugs and is down to one or two drugs.

Next slide.

As you can see, we haven't tracked very many.

Next slide.

But our problem really isn't that big for the size of our medical center. Again, this is the slide of the carbapenems.

Next slide.

As you've already discussed earlier on and probably will discuss later on in this meeting, there's virtually no gram-negative rod on multi-resistance drugs in the pipeline currently. In many facilities, there's an EIN questionnaire that's out electronically this week -- or actually at the end of last week, on whether people are back to using polymyxin B and E; E, being colistin. And certainly we are back to using colistin. We're out of drugs; we're using colistin. Colistin is an awful drug. It was replaced by the aminoglycosides because it was -- the immunoglycosides were less renally toxic and had less neurotoxicity. These drugs cause about a fifth to a quarter of people to have significant neurotoxicity.

Next slide.

And this is really the main data slide I brought after all of that. This is the data slide that we have at BAMC to support that we got a problem. And that -- and that the EIN is asking all of its members the same questions, it seems to be a nationwide problem. And basically in the years before 2000 -- before 2001 there were no patients that received colistin as a drug. In 2001 there were three patients, two patients, zero, four patients thus far this year.

Next slide.

Again, I don't have great data, but I'm not sure what we're going to do when we run out of drugs. And anecdotally I have had one trauma patient this year that did run out of drugs, and we stopped all of his drugs except for fluconizol while he was febrile, tachycardic, and somewhat hypotensive in the surgical ICU. He has survived, actually, but he was out of drugs. He got to the accumulated state where his plural fluid bug and his belly bug and his sputum bug and warm blood culture bug perhaps were not out of drugs, but in combination there were no other drugs that would actually cure him. We have no deaths yet. Certainly we are following the JCAHO Sentinel Events mandate, working up anyone who dies, looking for infections, and doing a root cause analysis if we see this. We have not done any of those since that has been implemented about a year ago.

Next slide.

So in conclusion, do we need new antimicrobial agents? Yes. Are we adequately tracking the problem? I think with the nosocomial MDRO GNRs, we don't have a firm hold on the problem at this current period in our hospital. And that's it. Any questions?

Next slide.

DR. OSTROFF: Thanks very much. Let me open it up to any questions or comments.

Dr. Gray.

DR. GRAY: This is Greg Gray. I'm wondering if the JCAHO requires all independent treatment facilities to have an infection control program?

DR. HOSPENTHAL: One more time.

DR. GRAY: Do all MTFs -- are they required by JCAHO to have an infection control program?

DR. HOSPENTHAL: Yes.

DR. GRAY: So every MTF collects data. And it seems to me that much of the data that you presented is very similar to the civilian data. The question I have is, how do you share between MTFs the data that you're collecting? Is that done in a systematic way?

DR. HOSPENTHAL: Only when data is filed through PL, which would be more like a reportable tracking, as in the CDC reportable agents.

DR. GRAY: So you don't really know what Walter Reed is saying to you --

DR. HOSPENTHAL: No.

DR. GRAY: -- and have no clue? Well, that -- it seems to me that -- in answering General Peake's questions should we develop new antimicrobials, with respect to surveillance, we're doing a heck of a lot, but perhaps we're not sharing that information between MTFs.

DR. HOSPENTHAL: That is correct. And even -- even those not required to do JCAHO actually do. The general hospital in Korea does JCAHO, even though they're not required to be accredited. So everyone's doing this; everybody's collecting lots of data. Like I said, the microbiology folks correct all this data. They have all of the bugs and all the Vitek results of every recovered organism, and they -- and they stockpile that data and it goes really nowhere.

DR. GRAY: And going back to John Herbold's comment, then if the -- if the MTFs, the in-house experiences are pretty well covered through your systematic infection control, then that leaves us, if we're looking at filling out the box here -- what about the outpatient antimicrobial resistant -- resistance that we would be concerned about, such as what John said, the (inaudible) and other outpatient treatable things? Do you see any big gaps there from your clinical perspective?

DR. HOSPENTHAL: Well, all the cultures from inpatient and outpatient are tracked in the same fashion. Certainly infection control doesn't get involved with the outpatient collection. And many of the -- many of the outbreak studies are really spot studies. The gonorrhea problem, the CDC actually came -- came to Hawaii and asked that our -- the military MTFs started culturing folks and collecting data for them, collecting resistant isolates. And so they're more of on a problem-to-problem basis that those are investigated. And so, you know, when the specific strains of fluoroquinolone resistance first started cropping up in the pacific and on the west coast of California. We actually did collect -- we stopped doing gene probes and started doing cultures in some of our STD clinics.

DR. OSTROFF: Let me question and play a little bit of a reverse chicken little. It actually looks like your data are somewhat on the reassuring side. And given the patient population at BAMC, particularly burn patients and things like that, I'm curious as to what you've been doing right to not have major problems with organisms like VRE and MRSA, et cetera.

DR. HOSPENTHAL: Well, that was actually my conclusion when I started putting this together. The infection control program is a high priority with the command, and it's a very strong program. And really for a -- we don't

do bone marrow transplants, we don't do solid organ transplants, but we fly in people from around the world for burns, as you said. We are a trauma center, so we take civilian trauma from throughout the city and share that with Wilford Hall and the university, and we do have some broken up people with dirty injuries, either from war or from trauma, who actually do quite well, surprisingly.

COLONEL DEFRAITES: This is Colonel DeFraites. I have a following question to that. It wasn't clear to me what -- which of those patients were the burn patients in the burn unit and whether or not -- if they're included in that data, if there are any particular patterns that would separate and distinguish them from the other patients?

DR. HOSPENTHAL: Not particularly. The burn -- the unit itself is actually very, very strict as to infection control policies, probably fourfold more than the hospital itself. Everybody basically is in contact, and special precautions, everybody gowns, gloves, booties, up -- puts on sterile gloves to go into each of the rooms in the burn unit. So there hasn't been a large problem there. And it's -- I would say anecdotally -- certainly the data is actually broken up, and I didn't bring those slides. But the data does follow fairly closely. It is tracked individually by a unit and specifically by a burn unit versus the other units. At least for the identifiable -- what infection control generally does

through the JCAHO and CDC guidelines is they pick out the things that they should be following rather than spend their time doing things that they can't -- they don't have personnel to follow. So it's certainly -- our main things are lying infections, BAPs, and specific organisms, such as (inaudible), VRE, and MRSA. And with those we do track each of the intensive care units to include the burn unit as a separate intensive care unit.

There really hasn't been a lot of long-term differences. Certainly for a while we'll have one unit that has more lying infections and then we'll go back into that unit and stress the use of full barriers and gloving and gowning and that will come back down. But nothing that really is -- we don't have an acinetobacter in one unit and a pseudomonas in one unit. And overall anecdotally, again, I would say that out multi drug-resistant pseudomonas problem is chiefly seen in the trauma and surgical ICUs, where people from the trauma side of the house (inaudible) traumas off of dirty wounds often with prolonged stays seem to accumulate resistant organisms; where as in the burn unit, it's less common, even though they have very protracted stays, the infection control is at a lot higher level.

DR. OSTROFF: We'll take two more comments, and then we have to take a break first. So Dr. Gardner and then Dr. LeMasters.

DR. GARDNER: It sounds like you're doing a very good job in your infection control program at keeping the rates low and steady. The concern I took out of your presentation, we've always at least hoped that the resistant organisms were at a competitive disadvantage and not as strict, and if we reduce the selected pressure, we would tend to have -- things would get better. But you now have this PVL in your MRSA, and PVL, which is a -- a pathogenic advantage linked to your -- to resistance somehow. And are actually on the same bit of DNA, or are they separate -- is your resistance separate from your PVL gene phage and -- I wasn't quite clear on that.

DR. HOSPENTHAL: Yeah, it's all --

DR. GARDNER: If you put those two together, you have a bad situation potentially. So like our flu where we're worried that the avian flu will pick up by a transmission factor.

DR. HOSPENTHAL: I don't believe that they're actually linked or the same package, but they seem to have become associated. I think the mec IV and the PVL on the phage are actually different. Don't quote me on that. I have a couple of fellows who do most of that.

DR. GARDNER: So it's worrisome; you're to be congratulated that it hasn't happened, that the numbers haven't increased.

DR. OSTROFF: Last word Dr. LeMasters.

DR. LEMASTERS: Well, at several of our meetings, we've talked about new drugs in the pipeline and a big concern about this. And it seems like one way to get some money put into this direction is to do a cost-benefit analysis. And I just wondered, has we -- have we -- do we have any cost-benefit analysis of what is the current cost for having antimicrobial resistance in terms of lost duty time, time in the hospital, medications, also with the related families and their illnesses? I think that it must -- costs must be very large with this situation, and I can't understand why we know that there is a train coming down the track about to hit us and, you know, we just can't get money toward developing these new drugs.

DR. HOSPENTHAL: I think some of that is really in how we do the analysis and how difficult the analysis is to make. And I'm saying that the multi drug-resistance pseudomonas is in my trauma patient who had a dirty wound and 16 fractures from downtown who has been in the ICU now for weeks to months is just like the MRSA data -- the old MRSA data from nosocomial infections, is it that the substrate is there, is the patient so sick that they have been in so long that they have this multi drug-resistant bug, or is it that the resistance is causing the prolonged hospitalization? I think that's hard data to work through; it's hard data to

research and to get out -- to tease out of the multi factorial setting.

And that's also been -- that's been the problem in the last two decades, the argument whether of nosocomial MRSA is more a virulent pathogen. And probably the overall consensus, though there's people on all three sides of more virulent, less virulent, and about the same as regular staph, most people actually lean towards it's less virulent. It carries around a lot of extra genes and it really incurs in people who are -- have been in the nursing home forever and have gotten a thousand courses of antibiotics, who have become colonized with this more resistant MR -- this more resistant staph aureus. And perhaps it's just they're so sick that they're the ones that needed the line who got infected, et cetera, et cetera.

DR. OSTROFF: Very good. I'm going to take the moderator's prerogative to move us towards our break. It's -- on my watch, it's just about 25 of 10:00. Why didn't we take a ten minute break and come back at a quarter of. We have a couple of more presentations after the break on this topic, and then we'll have some discussions. Thank you very much.

(RECESS FROM 9:36-9:47)

LT. COLONEL CHRISTOPHER: We're going to discuss how we define epidemiologically significant organisms, the antibiogram, and use of our computer assist. Essentially

this computer-based program is coupled with very active (inaudible) epidemiology from our infection control practitioners.

Next slide, please.

Essentially we define our epidemiologically significant organisms per definitions from the National (SHEA's), et cetera. Also we take note of regional trends in antibiotic resistance, what organisms are of importance in San Antonio, in the South Central United States, and finally in our own local data from our own specific hospital.

Next.

Okay. So as in many tertiary hospitals, we're seeing problems with resistant gram-positive organisms, MRSA, and, as we've heard earlier this morning, about half of our cases in our hospital are MRSA. Vancomycin resistant enterococcus to a lesser degree. Certainly the (inaudible) is very high on our radar screen. We're certainly -- currently in the midst of an epidemic. Multi drug-resistance gram-negative organisms we define as being resistance to two of three of these antibiotic classes. We lump beta-lactams, monobactams, and carbapenems as one class and aminoglycosides and fluoroquinolones. In our experience we see multi drug-resistance pseudomonas, enterobacter, and Stenotrophomonas as the main problem of gram-negative organisms. Acinetobacter has only emerged recently as a

significant pathogen in our hospital.

Next slide, please.

So we have several different systems with built-in redundancy in order to identify patients infected with multi drug-resistant organisms. The first step, the microbiology lab alerts the infection control program when a significant organism is isolated. This is a person-to-person telephone contact. If the organism is identified over the weekend or on a holiday, they call the infection control phone number and leave a message on the -- on the answering machine so that the team picks it up on the next workday. The infection control program, however, has a separate system -- again, built-in redundancy -- a computer program, the extended antibiotic resistant protection, or ERD program, which interfaces with the CHCS. That's our main clinical laboratory data bank that clinicians access, you know, every day while caring for their patients. So that interface detects antibiotic resistance -- resistant organisms. This is a homemade in-house developed program, developed by our information systems, our computer folks, in conjunction with our infection control team. So when patients are identified by either method, they are flagged in CHCS as being colonized or infected by a multi drug-resistant organism. And that goes up front on the demographics, so that when they are then readmitted -- whenever their CHCS file is accessed, that

information that they are colonized with a resistant organism comes right up to the front of the page so that the infection control program will be notified and that contact isolation or other appropriate isolation measures will be implemented. The infection control program then starts a file specific for that patient and continues active surveillance until either the patient is discharged or until they are proven to be no longer colonized or infected. And, again, if the patient is then readmitted, the admissions clerk pulls out their CHCS file, the flag comes up, colonized with a resistant organism, so they go into isolation and surveillance continues.

Next slide, please.

This is an example of a printout from the ERD computer program. Essentially the patient is identified using, like, a name, their patient number, the culture date, the specimen, and the particular organism. Again, these being multi drug-resistant organisms, the computer program to select out only those of significance by our predetermined criteria.

Next slide, please.

This is an example of the resistant isolate, the organism, the susceptibility profile, either resistant, susceptible, or not tested.

Next slide, please.

So how do we define -- or how we engage outbreaks? Essentially we define clusters as three or more

cases in the same geographic location within the past month, an outbreak greater than expected incidents, and, finally, rising endemic breaks.

Next slide, please.

So, essentially, if we identify a cluster outbreak, et cetera, we assess the location to rule out -- rule out the cluster. We try to identify any factors contributing to the outbreak, lapses in infection control program, et cetera, and certain other factors. We -- we're going to get to the specific problem of our CWCL epidemic in a few minutes, and we'll discuss some of the hypotheses that we have regarding the emergence of that pathogen.

Okay. Here's our C. diff. These are C. diff rates per 10,000 occupied bed days. Now, this data is compiled by our infection control program through the use of the ERD computer program, plus they run -- they prepare these charts that calculate the rates. And we can see that we have two apparent peaks here, last winter, and current -- and now currently.

Next slide, please.

This is the same data further refined. This shows our mean incident rate of C. diff colitis one standard deviation -- two standard deviations up, again, showing these two peaks up here in our current epidemic. Now, these two peaks were found to be related to clusters. Two separate

clusters in two specific areas of the hospital, ICU and the medical ward. So robust infection control measures augmented. The epidemic went away. Now we have no particular geographic cluster. Our cases of C. diff colitis are now scattered all around the hospital suggesting that there may be other factors involved.

We now have two leading hypotheses. One being that the alcohol-based hand hygiene products do not inactivate the spores. We're wondering if our use and heavy emphasis on alcohol-bases hand hygiene products may be partially responsible for this epidemic. The second factor, during this interval, our antibiotic formulary changed, our quinolone changed from amifloxacin to gatifloxacin. Now, gatifloxacin has more activity against anaerobic flora, so I'm wondering if this alters the gut flora thereby enhancing -- or decreasing colonization resistance, and this potentially will factor in our recent epidemic.

Next slide, please.

Now, we developed an antibiogram essentially patterned after the University of Texas Health Science Center approach. Dr. Jorgensen, the former chair of NCCLS, was very instrumental in developing this paradigm. Essentially we express the percent susceptible to any particular -- or specific organism. We do not report intermediate versus resistance, only in fully -- only fully -- the rate of full

susceptibility. We have separate antibiograms for inpatients and outpatients. We gather the data over a 12-month span. We update our antibiogram every six months using the data acquired during the previous 12 months. We sensor some of the bug drug combinations.

Next slide, please.

This is our inpatient antibiogram. And you -- essentially we only include organisms if we had ten or more isolates within the previous 12 months. So, in fact, acinetobacter only recently made the line up. And here are the rates of susceptibility. And, again, certain combinations or certain drugs censored. For example, enterobacter cephalosporins, we just put NR, not recommended. For pneumococcus, we don't report fluoroquinolones. So for the clinician in the middle of the night uses this user-friendly antibiogram, selecting the antibiotic by alphabetical order rather than by drug category, and then using -- or hopefully this will direct them to use the appropriate antibiotic that we would use based on our clinical background rather than simply in vitro susceptibility.

Next slide, please.

Now, how do you develop the antibiogram? Well, this gets into the third computer program, which we feel is really the backbone of our computer-based laboratory surveillance. This program is known as The Surveillance

Network. This is an Internet-based program. This is extramural, a civilian, commercial product that Wilford Hall has been using since 1992. And essentially our CHCS program feeds data to their computer every single day with our culture results vis-a-vis these patient -- with a unique patient identifier, a number which is independent of their Social Security number or their hospital identification number, thereby maintains confidentiality and maintains all HIPAA requirements. The computer receives information regarding the patient's age, gender, their location in the hospital, and the source, the specimen. Now, the information that is delivered to this computer can be tailored by a particular participating institution. There are, in fact, over 500 participating hospitals throughout the world participating in this program. Now, we can then go into that computer and pull up rates vis-a-vis incidents of resistant organisms for a specific time frame, for a specific antibiotic resistance pattern, for specific specimen sites, et cetera. Very, very user-friendly.

And we have some examples that I would like to show you. Now, we do have access -- well, we can access our hospital's information, but our hospital only as a specific individual hospital. So, for example, we cannot access information from BAMC, we cannot access the information for the University of Texas Health Center here in San Antonio. We can access by individual hospital, by region, so South Central

United States, or national. So we compare our rates of antibiotic resistance only to regional as a whole or the United States as a whole.

Next slide, please.

So this slide emphasizes the interface between the CHCS computer and the TSN computer. Next -- they notify us if they do not receive a report on a given date. For example, if our computers go down, they cannot receive a report, they will telephone us and tell us, "Hey, we did not receive a report for today. Will you please fix it." So we have good communication both ways.

Next slide, please.

This is an example of the type of data that can be obtained within a few minutes using this program. You can go ahead and say, "How many isolates or acinetobacter baumannii have we had in the past year," and it will give us a report by numbers of isolates. Essentially once a patient turns up positive, that particular patient will only be counted once by a site for every five days. So that thereby reduces the duplication and thereby inflation of those numbers. So we can get this data taken either bar graphs, line graphs, pie graphs, in a number of formats. And, again, this information can be obtained very, very rapidly. This is reported in numbers of isolates, however, not in rates. We have to calculate our own rates. So we can study trends and

hopefully the impact of specific interventions. So, for example, vancomycin-resistant enterotoxin. We decided, okay, we're going to put in a vancomycin order sheet. That any physician ordering vancomycin for their patient must fill out this specific order sheet that has indication. They must check the box, suspected MRSA, pencil in allergy, prophylaxis for certain orthopaedic procedures, et cetera. So they have to go through the thought process before they order vancomycin. Could this lower the use of vancomycin and/or hopefully the prevalence and the incidents of VRE in our hospital? So we just -- we go into the TSN program, and they will provide within minutes a nice graph of our percentage of VRE among total enterococcus isolates by time. So we began the printout here, and we can see that looking at the rates for the entire hospital, there really has been no statistically significant change in our VRE rates for the hospital.

Next slide, please.

However, we can refine that further going into medical ward plus ICU. Okay. Still no statistically significant impact.

Next slide.

But if we look at the ward -- at the ward patients, not ICU, that there has, in fact, been a significant drop. So we have made some progress, small steps. Key point,

we're able to follow that -- we're able to determine that by use of this computer program.

Okay. This shows the rates for the ICU. At this juncture, still no significant change. So we know where we need to target, where we need to focus for enhanced infection control practices.

Next slide, please.

So this shows the number of VRE in our hospital. And, again, this will break it down by outpatient versus specific location in the hospital, ICU or not. This graph shows us only the numbers. Again, if we want to calculate rates per 10,000 occupied bed day, we do that ourselves.

Next slide, please.

And so this shows, in fact, those rates that, again, our infection control teams calculates these and they're on information statistical patterns.

Okay. Next slide, please.

So essentially when a patient is identified as being colonized with a heavily resistant multi drug-resistant organism, they go into the appropriate isolation contact and other measures as indicated. They are tracked by the infection control program until they're either discharged or proven to no longer be colonized or infected.

Okay. Next slide, please.

So any comments or questions at this juncture?

DR. OSTROFF: Thank you very much. Let me open it up to questions and comments. All I can say is that when I need some surgical or medical procedure, this sounds like the place to come because both Wilford Hall and BAMC seem to be doing a great job in terms of antimicrobial resistance.

LT. COLONEL CHRISTOPHER: Thank you, sir.

DR. OSTROFF: Greg.

DR. GRAY: This is Greg Gray. Could you give us an idea of how many of the perhaps over 100 DoD MTFs participate in the surveillance network?

LT. COLONEL CHRISTOPHER: I am honestly not aware of how many of military MTFs participate in the TSN network. I know that a launch tool is considering coming online.

DR. GRAY: What about the other networks that are available? I know there are antimicrobial resistant systematic programs. Are any of the other MTFs participating in those, drug sponsored or otherwise?

LT. COLONEL CHRISTOPHER: I don't know. We don't have that knowledge right now.

DR. GRAY: Does the Air Force --

COMMANDER WHITT: If I can be of some assistance.

DR. GRAY: Yeah.

COMMANDER WHITT: There are three MTFs that are currently participating in TSN and Wilford Hall, Treckler out in Hawaii, and Keisler Air Force Base in Alabama. (Inaudible) is in the process of doing its software configurations. So they should be on Board before the end of the year. And I'm talking, in fact, on Monday with Navy Bethesda in Maryland.

DR. GRAY: It seems to me that perhaps all, whatever it is now, 100 MTFs probably have an infection control program, and they probably have -- many of them have unique programs, such as yours, that do some wonderful things that find things that are of interest broadly, not only to your treatment facility. Is there a czar that you report to such that other MTFs can benefit from what you're finding, or is it all held internally?

LT. COLONEL CHRISTOPHER: Well, this is our own (inaudible) program, which makes for a very robust use of an extramural computer program. That's essentially our -- I think that in this day and age of the air vac and bringing patients across the Atlantic, we have our air vac system essentially accelerating the process of microbial traffic. So I think connectivity is really a very important concept that we need to amplify and develop, communication between the various MTFs.

DR. GRAY: Exactly my point, that there's not a lot of communication.

LT. COLONEL CHRISTOPHER: Right.

DR. GRAY: And perhaps because not everybody is going to be embraced by The Surveillance Network. I mean, the thought of bringing on another 100 surveillance centers and getting them all free computers, the thought of that is going to challenge the system. You're going to have multiple different strategies from all these MTFs. And so, you know, the question is, in order to develop new antimicrobials and continually monitor antimicrobial resistance among pathogens, how do we do that in an efficient way without new personnel? One idea that comes to mind is have periodic access to DoD reporting systems, much the same as we've seen with the CHIP's periodic -- it's like the MMWR product or NHRC's GEIS newsletters, such that people that want to highlight the things they're finding in their MTFs could in a safe way, that doesn't offend a commanding officer, publish it so that other people could benefit. Because I sense that other than peer review journals, the information that you're finding in large MTFs is just not getting out. And when it does get out, it's probably a year old.

LT. COLONEL CHRISTOPHER: Well, yes, we need real-time information accessible by computer. So, for example, as -- well, patients leave launch toll with surveillance cultures, (inaudible) cultures for acinetobacter screening still incubating. So a patient comes in one or two

days, they're on a plane -- Walter Reed -- okay. We would pick up the telephone and/or e-mail, "Patient so-and-so heading your way with acinetobacter baumannii with this resistance pattern," you know, a day or two late. So they would not have access to our CHCS program. So in proving connectivity and communication, and specifically computer-based connectivity, really the -- an effective tool in this day and age of microbial traffic.

DR. OSTROFF: Other comments? One more.

UNIDENTIFIED SPEAKER: I guess partly my question is to Greg -- Greg as well. You say there are multiple systems that are out there that are like this -- like this dot-com system that (inaudible) creates. Is it -- is there a sense that anybody could just join any one of these systems or multiple systems? I mean, what's the -- sort of what's the ebb and flow with respect to this?

DR. GRAY: I only follow this loosely, but I know, for instance, Gary (inaudible) in our institution has several networks, sometimes exceeding 45 hospital facilities that send him different pathogens. And I know that -- is this (inaudible)?

UNIDENTIFIED SPEAKER: Yes, it is.

DR. GRAY: If you know that it (inaudible) multiple different of these networks and some of the strategies to get units to participate is not only to give you

a free computer and software but also to give you the interactive data feedback that obviously has kept them on Board for 12 years. But in the DoD, other than what NHRC is doing, there is no cross service, at least from a strep (inaudible) and Group A strep, assuming (inaudible), there's no cross service surveillance that I'm aware of.

DR. POWERS: I can bring this up in some of -- I mean, I'm going to show some of this data, and I'll talk some more about the various ones in my talk.

DR. GRAY: Because it seems -- just my comment, then, is that it seems that there's an opportunity for this to go sideways or to go in a productive way. And that is, that if people are just left to their own devices and opportunistically join any particular network or networks that they might, then that's not very productive. But the notion of collective movement -- because the technology supporting this is obviously relatively straightforward, relatively simple, not to say that it would be easy to implement. It would take a lot of work. But it seems like there's no real resistance to the concept of doing this, but it should be done in a rational, prospective, solid way. So I think, depending upon discussions, it might well be part of the recommendation.

DR. OSTROFF: Thank you very much Colonel (inaudible).

Before we turn it over to the next presenter,

there are some administrative issues from Colonel Gibson.

COLONEL GIBSON: Yeah. I need to get a count on the folks who are going to take the Lackland tour tomorrow. Now, that's an open tour, so any of us can -- anybody in the room can go who would like to go. So if we could get a show of hands of how many are planning to go, and if you could get -- if you have a wife that wants to go as well, raise two hands, or a spouse. That includes you-all in the back.

Okay the next one is for Zuni's Grill tonight. I need a show of hands for who wants to eat with us at Zuni's Grill, include your spouses if they're with us. Okay. Let's get that count. Okay.

UNIDENTIFIED SPEAKER: Does that include the martini cruise?

COLONEL GIBSON: I'll ask that question next. Okay. The martini cruise -- the Riverwalk cruise is -- we've got -- the boat will hold 28 people. So let's get a show of hands for that, how many would like to go.

Okay. Lunch is going to be on the veranda. We'll make that announcement again. And we have -- there's an in-house phone out here set up for us, and the in-house direct line for that phone is area code 210-352-3134. So if somebody needs to call you, they can call directly in there. To dial out on the phone, you dial nine to get out and you can dial your number. Area code 210-352-3134.

DR. OSTROFF: Okay. Our next presentation discusses what the research program is in the DoD around antimicrobial resistance, and we have Colonel Dave Vaughn, who is the director of the military infectious diseases research program and the U.S. Army medical and research and material command at Fort Detrick. Thanks for being with us.

COLONEL VAUGHN: Thank you, Dr. Ostroff. And good morning. I understand my task to be -- to overview the Military Infectious Diseases Research Program to let you know who we are, what we're working on, and then more specifically, to talk about our efforts in terms of antimicrobial resistance research, or perhaps lack thereof would be a better way to put it.

This title slide is meant to emphasize that while we are a tech base research program, our emphasis is very much on developing products to prevent service members from infectious disease threats, naturally occurring diseases. We're quite distinct in the biological weapons defense program. And also that we're triservice. The effort is Army led and funded through Army lines, but there are Army and Navy laboratories that participate and a scattering of Air Force officers located at those laboratories as well. So I'll try and give you an introduction. I know that many of the Board members are very familiar with our program, but this is something for you to consider in your recommendations if

you want to look at product development as a solution to this problem.

Next, please.

So our mission again is to conduct further DoD world-class infectious disease research to find effective means to protect our forces.

Next, please.

The first slide, I want to talk about some of our assets. The first would be our funding lines. Direct to the MIDRP programs is about $60 million each year. These figures are all for fiscal year '04. $40 million goes to our infectious disease research program. Another $20 million is specifically targeted HIV vaccine development. So about $40 million. Our advanced developer is USAMMDA, United States Army Medical Material Development Activity, and they have about $10 million for advanced development of products. Not very much for Phase III trials. Congressionally mandated efforts come through our office as well. In the past year, about $30 million. A lot of this is targeted to specific universities or companies, but some of it does come directly to our program, such as for HIV. The Navy also receives about $4 million this year for their agile vaccine program, which directly leverages our molecular vaccine efforts for malaria and dengue.

Other dollars, small business initiative

dollars. We were very successful this last year to compete for those dollars, about $3 million. Our investigators proposed topics for research. These are competed. Once they're selected, our investigators are involved in the review of proposals. So we have a fair amount of influence in which companies are funded for infectious disease research. Outside funding comes to our scientists, NIH, particularly for our HIV work, nongovernmental organizations, such as the (inaudible) Foundation and other -- and big (inaudible) industrial partners. We're just now looking at the total for fiscal year '04. I'm not sure exactly what that is. Something under $50 million.

Other DoD funded programs that help leverage commission of MIDRP include GEIS, which we've heard about already this morning, fund $9 million a year. The Navy has a prevention program for HIV among militaries in Africa and South Asia. And get a little more far afield are the biological weapons defense programs funded by DTRA and DARPA. We should have closer ties than we do with these groups, but when you get down to it, whether an infectious agent is delivered naturally or weaponized, a lot of the same technologies and principles apply in terms of vaccine development.

Next, please.

So that's the money. Bottom line, there is

about $40 million when we think about what's available for antimicrobial research. These are the place we work. In Fort Detrick is USAMRIID, United States Army Medical Research Institute of Infectious Diseases. This facility works largely on biological weapons defense, but it's -- a small part of their effort is on highly lethal viruses, primarily Hanta viruses at this time. Most of our investigators are located at the Walter Reed Army Institute of Research co-located with the Naval Medical Research Center in Silver Spring, Maryland. And to my way of thinking, the heart of our program is really our overseas laboratories; five of them. The Naval Medical Research Unit -- or Detachment in Lima, the United States Army Medical Research Unit in Kenya and Nairobi, the Naval Medical Research Unit No. 3 in Cairo, Egypt, the Armed Forces Research Institute of the Medical Sciences in Bangkok, Thailand, and NAMRU-2 located in Jakarta, Indonesia.

Next, please.

These are our 12 research coordinators. And this is the only slide I'm going to show that kind of oversees our portfolio of research and product development. So those 12 individual chair steering committees, which contain the subject matter experts, plan and execute our programs. They represent about 330 Army, Navy, Air Force, Department of Defense civilian and contract scientists of M.D. or Ph.D.

level.

So I'm going through this list here. First, a malaria drug program that's led by Dr. Wilbur Milhous, primarily prophylactic drugs but also some treatment drugs are being developed. Colonel Gray Heppner oversees our malaria vaccine program, both falciparum and vivax vaccine development efforts. Dr. Denise Doolan, just recently appointed, to oversee the malaria genome project. This group with their partners completed the complete sequencing of the malaria falciparum parasite and also vivax malaria and the mouse malaria (inaudible). Malaria, overall, is our largest program. Working on drugs, vaccines, more basic science and genome. If you include our work on diagnostics and vector control, almost half of our dollars currently go to malaria research. Our next largest program would be diarrheal diseases. Captain Steve Savarino heads this up, the (inaudible) pathogens. They focused on our (inaudible), campylobacter, and shigella. Colonel Wellington Sun heads our flavivirus vaccine development program. The focus here is dengue vaccine, and we do have a vaccine that's in advanced development. Lieutenant Colonel Russ Coleman oversees the diagnostics group. We've increased their funding a bit, but they really should receive a lot more funding. This is an important issue for DoD. But they're kind of changing their approach to get more diagnostics licensed in the U.S. for use

by our forces. Insect vector control, Colonel Scott Gordon oversees that. A smaller effort in rickettsial diseases. The focus here is on scrub typhus vaccine, and Dr. Alan Richards oversees that program. Dr. Connie Schmaljohn, our highly lethal viruses program. Her focus right now is to develop a vaccine on Hanta virus or hemorrhagic fever with renal syndrome. And they have a very promising DNA vaccine that looks very good in monkeys and other animal models. They're going to Phase I testing soon. Meningococcal vaccines, the focus here -- Dr. Wendell Zollinger and his group is on a Group B, as the military has previous ACYW135 vaccines. Colonel Alan Magill heads up our recently revitalized leishmaniasis research program. The focus there is on diagnostic and treatment that could be used overseas. And finally, with kind of their own funny stream is our HIV research program headed by Colonel Debbie Birx.

Next, please.

We have other assets. This is supposed to be a rather clever video of some monkeys, but --

MS. BENNETT: Oh, it came through as a separate file. Do you want me to --

COLONEL VAUGHN: No. Not now.

We have -- all of our laboratories are accredited lab animal facilities. Very valuable is our pilot vile production facility, where we can make vaccines for

Phase I and Phase II testing. Our Biosafety Level 4 containment has already been mentioned. Other laboratories have BL3 laboratories. And each of our laboratories have clinical trials units to conduct studies from initial Phase I through large Phase III efficacy trials.

Next, please.

So with these resources in terms of budget and geographic locations, people, we've had remarkable success, I would say, with six licensed vaccines where this program has had a primary role or important secondary role to bring these to licensure in the United States. I understand that within our malaria drug program that all -- they've played a role in all but one of the malaria prophylactic and treatment drugs in the United States at this time. And other products such as diagnostics, DEET developed with the USDA some years ago.

Next.

So what is MIDRP doing about antimicrobial resistance? And the answer is very little. We do collaborate and put into collections and characterizations of resistance strains of malaria and diarrheal bacterial pathogens, but this is primarily done through the GEIS program. As mentioned, we do have a vigorous program to bring new antimalarial drugs, and resistance there is certainly a huge issue. We've been very successful in that area partnering with nongovernmental organizations and industry. And outside of the Military

Infectious Diseases Research Program, the Combat Casualty Care program also has some efforts to work on antimicrobial peptides, primarily for dental (inaudible), but other topical approaches to reduce wound infection that can be applied at the time of injury.

Next, please.

So a short list of issues related to antimicrobial product development. First, the primary goal of MIDRP research is to prevent rather than to treat diseases. We do some treatment efforts, but 90 percent of our program is focused on preventing illness rather than treating it. Second, the DoD is not making new antimicrobials for bacterial pathogens. We do not have a program. And as we've heard, the interest and effort of big pharma is also reduced. Third, the DoD does have in place the people, infrastructure, and a successful track record for antimicrobial drug development. We've done it with our malaria drug program. And we've spoken to the leaders of that program about how difficult it would be to change to an antimicrobial effort. I was surprised to hear not very difficult at all. A lot of steps are very similar. It's just a matter of changing your targets in your computer programs. It doesn't seem that easy to me, but that's -- that's what I was told.

Next is the problem of antimicrobial resistance, you know, DoD specific or unique, and how would we

rank this compared to other problems of malaria, dengue, diarrhea, the need for improved diagnostics where we're putting limited resources at this time. I've already mentioned that the MIDRP is modestly resourced at about $40 million with really an extremely broad portfolio that surpasses many efforts in big pharma. And drug development costs are enormous. Depending on who you read, $300 million, $500 million, $800 million, over a billion dollars for one drug in 15 years. So it's a huge undertaking. We've had a lot of success with our malaria drug program, but I would point out that a lot of the products have been licensed in the last ten or 15 years came out of research that started in the '70s with Vietnam. There was a big push for antimalarials. And while we fund malaria drug at about $9 million a year currently, they were funded in excess of $70 million a year at the time that those products were really going through the pipeline. So we're talking about a lot of money to do more than what we're doing now.

And next slide, please.

So what might the MIDRP offer. These are just some suggestions for the Board to consider. You may have your own ideas about what we could do or what we're not capable of doing. We certainly can continue to partner with GEIS to document developing resistance within our current areas of research, primarily malaria, bacterial pathogens that cause

diarrhea, and scrub typhus by working through our overseas laboratories. Possible new efforts are listed here. Explore mechanisms of resistance to include bacterial physiology, functional genomics, and proteomics, and a fair amount of experience in this area could be targeted at antimicrobial resistance. Develop resistant specific bacterial diagnosis. We've heard a little bit about this this morning. We have been talking with a company that has a multiplex PCR for diagnosing clusters of etiologies for respiratory diseases, for encephalitis, and for causes of diarrhea. They're interested to pursue a rapid three-hour diagnostic for resistance. So you not only know what the organism is, but you would be able to more specifically target your antibiotics, and this might decrease the development of resistance. We would consider developing vaccines for common wound pathogens, a huge effort. This could perhaps be justified for some organisms like methicillin-resistant staph aureus. For others like acinetobacter and others would be a little hard to justify based on the frequency of these kinds of problems, but it could be considered.

What got us started on this question from the Surgeon General was wound infections and resistance. We could help to coordinate prospective pyophylactic treatment studies in Iraq or trauma settings. Very difficult to do, a lot of variables, people get injured or wounded at different places

at different times, different times of care, different types of care. I understand it's been difficult just to get medical records out of the country with the patients. Also combatant commanders in the theory of operations don't like researchers running around exposing themselves to being wounded themselves. So it's difficult to do this type of research. Develop new antimicrobials. We've been talking about that possibility. A little more exploratory, higher risk type research, such as what DARPA is doing now, to look at immunomodulatory approaches to disease prevention, products that could prevent any number of infections by a large number of pathogens. The bottom line, any new efforts would require new funding, more personnel, and as we do with all of our existing programs, extensive partnerships with federal and nonfederal groups of researchers.

And my last slide.

To summarize the MIDRP, we contribute to the defense of the United States and to the needs of people living in endemic areas and travelers to those areas by developing drugs, vaccines, and diagnostics, providing a better understanding of many tropical diseases, and through our overseas laboratories, we have contributed greatly to the development of research infrastructure in many developing countries. And antimicrobial resistance is a new challenge, and what our role, if any, should be is in large part left to

this Board. Thank you.

DR. OSTROFF: Thank you very much, Colonel Vaughn. Let me open it up to any comments from members of the Board.

(Inaudible.)

UNIDENTIFIED SPEAKER: My question is, what establishes your priorities? I mean, what is behind the list of areas in your portfolio?

COLONEL VAUGHN: How do we decide our priorities for research? Some of them are rather time honored. Malaria, dengue, diarrhea have been problems for every military engagement we've had back to George Washington, and continued to extract rather large costs when we -- when we deploy. We have a requirements mechanism through the AMID center and school, for example, for the Army, which is located here in San Antonio. And they request or provide requirements, things that they -- problems that they would like to see solved. And so part of our direction comes from that group.

But we're looking at a little more possibly objective approach to prioritizing our efforts correctly. We're working with AFMIC, the Armed Forces Medical Intelligence Center. And they quantify risks for every country in the world -- well, excluding North America and Europe -- for 64 infectious diseases. And so we're putting

together an algorithm that looks at risk of infection and uses a factor of severity, disease severity from an operational perspective, whether a person needs to be evacuated or they're just sick for a day or two. And we've put that together into a new threat list. We're not quite finished with it, but these are some of the (inaudible) we go to in thinking about what we're working on.

We also -- I have an advisory committee. We meet once a year to look at what we're working on, whether we should redivide the funding or work on new areas or eliminate them. This Board has also had input in terms of the type of research that we do in past years.

DR. OSTROFF: Dr. Cline.

DR. CLINE: The fourth-to-last slide, I think. Could we go back to that one?

MS. BENNETT: Sure.

DR. CLINE: What MIDRP is doing about antimicrobial.

DR. VAUGHN: Yeah, that one.

DR. CLINE: Yeah. I just wanted to raise a question on that item -- the third bullet, Combat Casualty Care Research. I think it is a very key area in terms of -- we think of the discussion we've had earlier today about microbial traffic and fun issues related to that rapid introduction and problems in acinetobacter and others. Could

you go into that in a little more detail? It seems to me we haven't given enough attention to that issue, antimicrobial peptides and other topical options and primary prevention and transmission.

COLONEL VAUGHN: I really don't think that I can. There may be someone else in the room that can address this better than I. I drafted this sentence and showed it to the director of the Combat Casualty Care Program and he agreed with it. And I really don't know much more in terms of specifics beyond what's here and that they are working on peptides that can prevent (inaudible). And that they're working on looking at surgical equipment prosthetic devices that are coded with peptides or other agents that could prevent infection. They're looking at hyper oxygenating compounds that could be applied to wounds early on to help prevent infection. They're talking about administration of antibiotics on the battlefield at the time of injury and at every point subsequently. Those are some of the things I know -- I hear them talking about when we're at the same meetings, but I don't know the specifics.

DR. CLINE: Are there --

COLONEL VAUGHN: It's both the prime issue and infectious disease issue.

DR. CLINE: Are there studies underway in the battlefield setting --

COLONEL VAUGHN: Not with --

DR. CLINE: -- with some of these interventions?

COLONEL VAUGHN: Not that I'm aware of. Anyone else? I know they're funding the peptide work. The rest is talk. I don't know if they're funding any specific research in those areas or not. They may be.

DR. OSTROFF: Dr. Shanahan then Dr. Patrick.

DR. SHANAHAN: I'm Dennis Shanahan. If I'm not mistaken, in order for your program to get involved with antimicrobial drug development, we're looking at not just an increase in personnel but a considerable increase in infrastructure as well. Even though you may have the technical capability within the malaria program, if I'm not mistaken, you would have to have quite an investment in infrastructure as well as personnel.

COLONEL VAUGHN: Yes. Unless the recommendation to eliminate our malaria drug program or replace it with an antimicrobial drug program, yes, we would need additional people and facilities and a lot of money to put forth a serious effort in antimicrobial drug development.

DR. SHANAHAN: And if I'm not mistaken, also that $40 million you're quoting is basically research dollars that does include personnel costs, infrastructure costs as well.

COLONEL VAUGHN: It includes all the personnel costs except for military. I'm not sure what percentage are military, 10 or 20 percent of the personnel in the program. There are infrastructure savings, maybe the buildings are paid for, and we don't have to contribute to that. Some we do. We pay rent for many of our buildings.

DR. SHANAHAN: Well, if that's the case, then a good portion of what your -- what you've got toward your program is personnel costs, because you list, like, 330 personnel, which I would imagine probably less than half are military.

COLONEL VAUGHN: Well, we're not paying for all of those people completely. Those are people who participate as investigators in the MIDRP program. They may get funding through GEIS or through an NIH program or through a (inaudible) company. There are many, many sources of income for the people that participate in this program.

DR. SHANAHAN: Okay. Thanks.

DR. OSTROFF: Okay. One last question before we get to our last presenter. The slide that lists all the licensed products that have come out of the MIDRP program -- it might be that people have to put their thinking -- did the military ever participate in the development of any of the major antibiotics that have been developed over the years.

COLONEL VAUGHN: You know, I heard at a

presentation last week chloramphenicol may be an indication for scrub typhus. But I guess the product wasn't developed by the military.

DR. OSTROFF: Yeah. Because, I mean, it doesn't strike me that I have any recollection that the military was a big player in any of the major classes of antibiotics, but I could be wrong in that. I mean, you just don't think of them when you think of antibiotic development.

Thanks very much. Our last presenter is Dr. John Powers. He is the lead medical officer for antimicrobial drug development and resistance initiatives at the FDA. I imagine in Cedar, if I'm not mistake. And we appreciate you taking the time out of your schedule to be here with us, and we look forward to your presentation.

DR. POWERS: Thanks for your invitation. It's always good to be the guy that's standing between folks and their lunch being the last presenter.

DR. OSTROFF: We're doing well on time.

DR. POWERS: Yeah, okay. That's fine. We'll get an early lunch then.

Actually, what -- I mean, this is -- it's really -- I enjoy coming to these things as well, because what I hope you'll do is ask me a lot of questions after this is over, because I think that we at the FDA are in a very unique position. And I have to say that what I'm going to give you,

too, is a lot of my personal experience with this in terms of I am still a practicing infectious disease clinician, and I still go to the clinic once a week and do the inpatient service once a year, as well as working at the FDA where I always paraphrase Yogi Bear that I'm 50 percent doctor, 50 percent lawyer, and 50 percent businessman. Because at the FDA we see where all of this confluence comes together of the economics and the science as well as the issues with regulation -- which my personal feeling is the regulation is the science -- there is no difference between those two. And the things that we ask for in terms of data really relate to the science.

If you'll go on to the next slide for me.

So what I'm going to talk today is about how do we get to this point. What's some of the history of antimicrobial drug discovery and development, and how is that impacted upon where we are today? And then the two big issues that really impact on antimicrobial development going forwards are economic issues and scientific issues and how those go together. And I'm going to make some pretty blunt statements about this today. And let me preface this by saying, there are no good guys and bad guys in this. If you work for the pharmaceutical industry, your primary job is make money for your company. There's nothing wrong with that. That's how capitalism works. On the other side of this, we've got us at

the FDA where our primary job is to protect and advance the public health. Hopefully those two things go together most of the time. Sometimes they don't. And then we'll talk about some of the future needs in antimicrobial drug development. And I'll relate this to the four points that Dr. Whitt talked about in the public health action plan, surveillance, prevention and control, research, and then product development.

So let's go back to talk about some of how did we get to the antimicrobial age in the first place? So the efficacy of antimicrobials when they were first introduced in 1937, penicillin was not the first antibiotic that was introduced, it was subcutaneous sulfanilamide. And what people originally used antibiotics for were serious and life-threatening diseases, things that people were dying of. So in the original study on subcutaneous sulfanilamide, it only included 10 patients in 1937. They compared that to the mortality of a 1906 outbreak in New York of meningococcal meningitis where the mortality rate was between 70 and 90 percent. Using subcutaneous sulfanilamides, something unthinkable today, they cured nine out of the ten people in which they treated. So you didn't need a whole lot of patients to show that the drugs were doing something in these serious and life-threatening diseases. But then what happened, as we look at the history of antimicrobial use, is

that based on this efficacy in serious and life-threatening diseases -- and one of the earliest ones was oral fluorfenicol for the treatment of typhoid fever, which the military was involved in -- clinicians started to use antimicrobials for less serious self-resolving diseases. Things like acute bacterial sinusitis, and this was based on the premise that if you get rid of the bug, the patient's going to get better. But what that didn't take into account was, gee, maybe the patient gets better even if we don't get rid of the bug. And so what we have is some clinical trials data that really looks at some things like ways to cure a disease that gets better in three days. And then that data becomes very difficult to interpret. So what it doesn't take into account is the human immune response and the natural history of some of these illnesses. And that becomes very important when we talk about clinical trials today.

So the issue here is that the majority of classes of antimicrobials were discovered by the end of the 1960s. So when you look -- the way we divided this up -- and a lot of what I'm going to say today will be published in an article in Clinical Microbiology and Infection in December. And we had a workshop on this in April of 2004 that the FDA cosponsored. And what we did was we looked back and we defined a class of antimicrobials as a drug that acts with an entirely unique mechanism of action. So it binds to a

completely different site. Therefore, if you use that classification, new drugs like telithromycin are not a new class. They are (inaudible) of the macrolide class of antibiotics. And I'll show you a graph on here that's coming up that says that really the majority of drugs were already discovered. By 1968, we had discovered ten of the 13 classes of antimicrobials that are available today. What most people also don't realize is that 1938 was the Food, Drug and Cosmetic Act that actually gives us (inaudible) FDA that said people had to have safety information before they could market their drug. The reason why that occurred was because of an antibiotic. Sulfanilamide, which was not soluble, was mixed in with Diethylenglycol, essentially antifreeze, and given to children, and over 100 children died when they received this drug. And it was that impetus that actually resulted in Congress passing a law that said people have to show safety data. They did not have to show efficacy data. And it wasn't until 1962 when folks in Congress said, "Listen, if the drug's not doing something for somebody in a positive way, there is" -- "then why should we risk giving anybody any toxicity on the other side?" And I think that's what underlies our appropriate use issues today. If a person doesn't have an infection or has a viral disease that won't respond to an antibacterial, what is the point of giving them an antibacterial agent? But -- since most of these drugs were

actually approved and on the market prior to 1962, they were kind of grandfathered in by the FDA, and therefore well designed clinical trials on the efficacy and safety are really often lacking in a lot of these diseases. And I bring that up because what we're -- what people referred to back in a lot of these discussions is they'll say to folks at the FDA, "Well, you approved penicillin this way." And what I try to point out to them is that penicillin was introduced in 1941, and the science of clinical trials has advanced just like the science of medicine has.

So here if you want to look at this graph, you see that the sulfonamides, penicillins, aminoglycosides, chlorophenicol, tetracyclines, macrolides, glycopeptides, like vancomycin, rafampin, nitromidazoles, like metranidazol, and quinolones were all introduced prior to 1962. So -- and then as we heard this morning, there is a big gap between 1968 and the year 2000. So when people talk about decreasing drug development, this is not a new problem. Coming up with new what's called scaffolds for antimicrobials, in other words, an entirely new class, has been a problem that's going on for 40 years. It is not new.

So why is it that we're seeing this decrease in drug development now and why is it coming up now? And actually there may be some good news out of this, because in the last two years -- three or four years, we've had two new

classes introduced, and so maybe we're going in the right direction. So the majority of drug development since the 1960s, then, has been alterations in previously discovered classes of antibiotics. Now that's necessarily a bad thing. We had a number of cephalosporins, et cetera, introduced; we've had drugs that have added beta-lactamase inhibitors to them which have increased the spectrum of activity of those same classes. We've also had changing in the pharmacokinetics of those drugs. For instance, we know that you can use the third generation cephalosporins to treat meningitis, whereas the penetration of first generation cephalosporins into the cerebrospinal fluid is not that good and you can't use them. So even though it's a member of the same class, we got some added benefits. And then there are differences in the toxicity profiles of the drugs as well, and we know this if we look at the fluoroquinolone class. There have been 12 fluoroquinolones proved since 1980, and four of those are off the market today because of toxicity issues. And let me correct a misunderstanding. None of those were taken off the market by the FDA. They were voluntarily withdrawn by the drug sponsor because they realized that when folks figure out your drug has toxicity, you can't sell it anymore. So unfortunately that gets misconstrued that the FDA is pulling these drugs off the market. So the majority of drugs in the 1980s were cephalosporins and the majority in the 1990s were

quinolones.

So if we go to the next slide, I'll show you some information on this.

So if we look at -- so if you look overall at this graph, you can draw a line here and say, "Gee, if there's a slight decrease in the slope" -- and I have to point this out. The idea of saying bad bugs, no -- or bad bugs, no drugs paper combines all these together and draws a slope that looks incredibly huge. I think it's actually much more -- much more information to look at this. And it does no good to point to 2002 and say there were no drugs developed in 2002, because that's really a skewed way to look at it. If you look at this, then, all of this yellow is all beta-lactam drugs. And, in fact, 24 of 29 drugs approved in the 1980s were beta-lactams. The vast majority of which were cephalosporins. Some of them are famous drugs like cefmenoxime, cefonocid, things that we don't really use clinically. So yes, there's a decrease in drug -- drug development overall since the 1980s, but is it really a decrease in useful drugs, or have we seen a decrease in the need-to drugs. And doesn't that kind of make economic sense, because once you saturate the market like this, how many more of these drugs do you need? And if you haven't been able to develop a new class of drugs, then you can see why we're in the position we are today.

Let me go to the next slide, then.

So let's, then, take out the cephalosporins out of that and look at what happens here. If you take out the cephalosporins, we've actually seen an increase in the number of drugs and actually more new kinds of drugs recently in the last couple of years. The problem, though, is that drug discovery efforts sort of ceased 20 years ago in the large pharmaceutical companies. So what we're seeing is that, are we going to continue this trend? Well, that's what people are worried about is that we don't have new drug discovery efforts. It's not that people haven't tried; it's that drug discovery has been very, very difficult. And the promise of genomic drug development at least in the antimicrobial era -- area has remained unfulfilled to date.

Let's go to the next slide.

So some large pharmaceutical companies have chosen to exit the area of antimicrobial drug discovery and development. And as I said, this is something that's been going on for 40 years. And many of these issues really are based on economic decisions by companies.

Let's go to the next slide.

So why is this? Well, antimicrobials are not as profitable as other drug classes, and you heard the big net present value discussion this morning. And I sit there and I take off the doctor hat and the FDA hat and I look at somebody saying $100 million is not enough profit for me, and I scratch

my head as a future potential patient and say, "Why is that bad? You're making $100 million on an antimicrobial." Well, the issue is the best-selling antimicrobial in the world last year made $2 billion and a lipid lowering agent made by that same company made $9 billion. If you're in business, which one of those are you going to make? So you can see from an economic point of view that it's much more profitable to make other kinds of drugs. Well, why is that? Well, first of all, there's a high level of competition with already marketed drugs. The vast majority of antimicrobials, about 80 percent of them, are prescribed in the outpatient setting. Do doctors really think resistance is a big problem in the outpatient setting? Well, a study two weeks ago in the archives of internal medicine done by folks at the CDC said doctors think that resistance is a national problem but it's not a problem in my backyard or in my institution. So part of the reason is we don't know whether it's a problem in the outpatient setting, because most people don't get cultured in the outpatient setting. The other thing is that antimicrobials are primarily short-term treatments. You give five days, ten days of an antibiotic, whereas you stay on a lipid lowering agent or an antihypertensive for the rest of your life. We talked about the lack of perceived need by clinicians, and if -- how can a company sell a drug for which there is not a perceived need? If folks don't think that they need it, why

should they develop it? The other thing is the greatest need is for less common diseases. There were 34 million prescriptions written last year for acute otitis medium in children. Hospital acquired pneumonia, on the other hand, which can be a lethal disease, there were 160,000 cases. So what we've been told at the FDA by pharmaceutical industry representatives is we need to have diseases like acute bacterial sinusitis, acute otitis medium, and acute exacerbations of chronic bronchitis as a part of the portfolio for our drugs or we're not going to develop it for these less serious illnesses. Now, what I want to point out, though, is all of this is the view from the large pharmaceutical companies, and they are the ones who have chosen to exit this area. They're also the ones you hear from the most. On the other side, our experience at FDA has been that, much like we would expect in a capitalistic society, when somebody pulls out, that creates an opportunity for somebody else to get in. What we're seeing is a lot of smaller biotechnology companies get into this area who are more willing to develop drugs with a smaller niche, such as in the serious hospitalized -- seriously ill hospitalized patient. There's a lot of other economic reasons for that, too. The largest drug company in the world has 10,000 pharmaceutical sales representatives. There's only 8,000 people that work at the FDA. So put that comparison together. As opposed to a smaller biotechnology

firm that we recently approved a drug for has 80 representatives. And why can they do that? Because they only need that many people to go to hospitals to talk about that in a serious hospitalized infection.

The other thing is appropriate use limits the market. And I think this is -- and we just saw an article that's going to be published in Regulation Magazine that says that both the CDC and the FDA ought to butt out of telling doctors how to use drugs appropriately because that's a disincentive to the industry. Well, there's two flaws with that argument. And the first thing is what we went back to the 1962 Kefauver-Harris Amendment. If a person can obtain no benefit from taking the drug because they don't have an infection in the first place, then why should they be taking that drug with all its intendment side effects and the broader population issue of resistance? So in other words, should we tell people to take drugs just because it positively affects the bottom line of a company? That wouldn't seem to be a good public health strategy.

So what are the scientific issues, then? Well, we've heard these claims of increased regulatory hurdles for antimicrobials. There are no increased regulatory hurdles for antimicrobials relative to other drugs. And that really reflects a misunderstanding of some of the scientific issues. What we've been asked is, "Well, why doesn't FDA just approve

drugs for pathogen-specific indications?" In other words, infections due to staph aureus. Well, the reason we don't do that is because it doesn't make any scientific sense. We know that drugs that can treat skin infections may do absolutely nothing for staph aureus meningitis, that a drug that treats a urinary tract infection may in no way affect a hospitalized acquired pneumonia, and, in fact, we just had a recent drug that we approved for complicated skin infections that when studied for community acquired pneumonia, including active to staph aureus, was not proven effective in pneumonias. So even though the drug looked like it penetrated into the lung, it turns out that the drug binds to the surfactant in the lung and there is no free drug available. How did we find that out? Nobody bothered to look at that until after the clinical trial was done. So if you just looked at in vitro information, you would think that drug would be great for that particular disease.

The other issue is that it requires a larger sample size of patients to demonstrate similar efficacy of a new drug to a controlled drug. This has been a big issue. So what people want to say is, "Well, if we expand the amount that our drug is allowed to be worse than what's already out there, we need a smaller sample size." In other words, if you design your trial to show that your drug is only 10 percent worse than what's already out there, you need a whole lot more

patients than if you design your trial to show that your drug is 20 percent worse than what's already out there. Is that okay? Well, would a clinician use a drug for, like, bacterial meningitis that may be as much as 20 percent worse than something that's already out there? That's a clinical judgment question. But we know that the benefit of drugs in meningitis is something like 70 percent over no treatment at all. Where this has become a big issue is in the less serious self-resolving diseases. So for instance, drug sponsors come to us and say, "I want to design a trial for sinusitis that shows that my drug can be as much as 15 percent worse than what's already out there on the market." We did an analysis of the 17 placebo control trials for acute bacterial sinusitis and showed that it may be that the benefit of antibiotics in acute sinusitis is as little as 4 percent. Well, how can you design a trial to show that your drug is 15 percent worse than a control when the control is only 4 percent better than the placebo? So essentially what you're saying then is that your drug is no different than a placebo. And that has been -- that has been turned into a regulatory hurdle, when, in fact, it's really a misunderstanding of the science.

The other issue is that resistant pathogens are just less common in these trials. And the running joke at FDA is, if you want to make something go away, just try to study it. That will make it disappear right off the face of the

earth.

The other -- and finally, the issue of the clinical impact of resistant pathogens is really less certain than these more common self-resolving diseases. We did an analysis of trials of acute exacerbations of chronic bronchitis, and we evaluated people that received the drug -- and the pathogen that was isolated from their sputum was resistant to the drug that they received. The cure rate was identical in the people that had a resistant pathogen treated with that drug to the people who had a susceptible pathogen treated with that drug. So that says either our diagnostic criteria are poor or the impact of resistance in these self-resolving diseases is small because the overall impact of antimicrobials in these diseases is small.

Next slide.

But here's the issue: What we've seen overall is a decreasing trend in new molecular entity submissions to the FDA. A new molecular entity is a drug with a completely novel structure. So it doesn't have to be a different class, it's just a new antibiotic. So ceftriaxone and cefotaxime are both new molecular entities even though they're both third generation cephalosporins. So when you look at this, this is all therapeutic classes. So this is not unique to antimicrobials. And part of this is, again, the exceeding difficulty and challenges in coming up with discovering new

drugs. So that's gone down overall across the FDA. But here's what's going to happen with research and development spending. It's gone up. Now, what is research and development spending? Some people argue that we can't really get a good handle on that number and that some people are actually including marketing into that, but in any case, we know that the NIH isn't doing that, and the total NIH budget's gone up, too, even though we've seen this number go down.

So FDA has undertaken several initiatives to streamline drug development for new drugs and antimicrobials in particular. One of which is called the critical path initiative. And this tries to get to the point of, where is all this money going? When you look at this number that gets quoted of $800 million to develop a drug, the biggest chunk of that is drugs that failed to actually get through the process and make it to market. So I always joke it's kind of if I went out and I bought a car and it broke down on day two, and then I went and bought another car and it broke down on day two, and I bought a third car and it finally runs, I would be including the cost of the two broken-down cars in the cost of the third car. And that's what we're doing when we look at that big number of $800 million. So the question is, why don't we get rid of the failed drugs earlier so it's not going to cost so much to move a drug forward? Which means we need to come up with better tools earlier in the drug development

process to pick out the drugs that are most likely to be safe and effective from those that are not. Where does the biggest amount of money go in a clinical development program? It's into the Phase III piece. And I was interested to see Colonel Vaughn's outline of the budget there. It costs between $10 and $20 million to do a large Phase III multi center clinical trial, and you can see from your budget that you're right at the edge of that already. So that's going to be very difficult to do some of those trials with -- at least within your existing budget. So the important thing is here, we need to balance these economic needs of companies with the primary goal of protecting and advancing the public health. So the FDA's had several meetings addressing these issues. One is, we tried to apply data from studies in one disease to support approvals for another disease. For instance, if a drug sponsor does a trial of community-acquired pneumonia, can we use that to support a study of hospital-acquired pneumonia? In the past, FDA's always asked for two studies per disease to show that it's reproducible. People always ask me, "Why do you do that? Why do you ask for two studies? That seems like an awful lot." And my reply is always the same. "So if I go run an ELISA in my laboratory and I do it once, I'm going to run out and publish in the PNAS? I don't think so." People always ask for reproducibility of results even in a laboratory experiment. We understand that that's expensive and difficult

to do; but, boy, if we want to do it in the lab, shouldn't we really be sure that these things are safe and effective in humans as well? But can't we get this from information of similar diseases? So can we use complicated intraabdominal infections as a way to look at complicated skin infections since the pathogens are very similar? So -- and then, finally, can we apply data from the efficacy and susceptible pathogens to support approval for resistant pathogens? So you have a new drug and it has very similar in vitro activity against both susceptible and resistant; let's just take staph aureus. Can't we look at how the drug works in methicillin-susceptible staph aureus and try to use that to support the data in methicillin-resistant staph aureus so that people don't have to go out and do separate trials on MRSA?

So the other -- so let me get back to what we're going to try to do going forwards in the future. So the FDA has obtained surveillance data from the same place you folks do, and that's the surveillance network of Focus Technologies. And I'll try to elaborate on this a little bit. So we use this to try to address the areas of greatest public health need in the United States. Focus looks at over 500 hospitals, as you heard earlier, 317 of which are in the United States, and some of them are in the military. Let me get back to this. Are there other surveillance networks? Yes, there are. The Focus network looks at 2.8 percent of all

the isolates cultured in the U.S. The other ones look at far fewer, down around .8 percent or below 1 percent. So there's a bigger capture with Focus than the others. How do we know this? Because when we put out the RFP for this, we looked at all the different ones and tried to look at which ones were the most useful for us. The other thing is that what Focus does is as long as you have a computerized database in your hospital, you can link into Focus and get that information. So -- and my personal suggestion to you is, if you could hook into the military treatment facilities with Focus, you would quite easily be able to get this information back. And it sounds like you're already going down that path. It's just putting in the work to get over the initial hump of filling out the paperwork, et cetera, to get your electronic system hooked in. That also means that you have to have an electronic system, like a Vitek or something, that actually will dump that information into the Focus Technologies' database. So what we did was we used the Focus data, which I'll show you in a second, to actually develop criteria for pathogens of greatest public health importance. Because the other question that got asked just in the previous talk was, how do you prioritize this? What are the important pathogens that you want to look for? So we presented this criteria to our advisory committee about a year and a half ago, and we had ten of them and then condensed them down into six and combined

some of them together.

So first of all, the organism is common enough in the population to warrant concern and to be able to study it. Vancomycin-resistant staph aureus has occurred in three patients to date. You will never be able to study it. It may become a problem down the line, but at the present time, it would be very difficult to do anything with that.

Two, is serious and life-threatening diseases. And this is where I think we have the biggest issues with industry. The folks in industry want to study the common outpatient illnesses, and yet the impact of antimicrobial resistance is the greatest in the sickest people in the hospital. But fortunately for us in the U.S., those people are not that common relative to the outpatient diseases.

The third thing is that the drug to which the organism is resistant is used in the disease. It's very interesting that an e. coli may be resistant to streptomycin; however, nobody uses IM streptomycin to treat a very complicated urinary tract infection. So knowing that information isn't very useful.

And let me point out to you where the biggest issue for this has been. Why do I care that a kid has penicillin-resistant pneumococci in their ear when the drug used to treat that is amoxicillin? And when we looked at the cross -- the cross susceptibilities, about half of the

penicillin-resistant bugs are susceptible to amoxicillin. So it doesn't make any sense to us to be talking about penicillin resistance in that setting when we should really be talking about amoxicillin resistance.

Finally, there's the big issue of few therapeutic options due to multi drug resistance, and I'll show you how we've looked at that.

And, finally, the big issue that we really need help with, and that's correlating in vitro resistance with clinical outcomes. We define "resistance" by something that happens in a test tube, where we mix something with medium that has absolutely nothing to do with what the site of infection is in a human being. And I learned this when I went down to Atlanta when the CDC had their community acquired MRSA meeting a couple of weeks ago, that when you actually test trimethoprim sulfa against staph aureus, it's done in a thymidine-depleted medium. Well, what does that tell me about somebody who's got loads of thymidine floating around in dead tissue at the site of their infection? Is the drug going to work there or not, and how do I relate the in vitro susceptibilities with what happens in a person? And that's why we need to do the clinical trials to actually figure this out. This data is very, very hard the come by. And that's one of the things that I would ask if you guys can help us to be able to do, you can get some outcome data on what actually

happens in people with resistant organisms.

Let's go to the next slide.

So how can we look at some of these organisms? Well, we looked at Focus Technologies. Only 27 taxa of organisms accounting for 95 percent of the clinically encountered species. That's a big cut right there. We can focus on those 27 organisms that we're most likely to see in human beings.

Next slide.

So how do we look at the multi drug resistance piece? Well, what we did was we came up with a system where along the Y axis here, we will look at the number of agents to which these isolates are resistant and put the same drugs on the -- I'm sorry, on the Y axis here, on the number of agents to which the isolates are susceptible. So if you look up here, then, in the top left corner, that means that all these dots here represent one isolate per patient, and these isolates are susceptible to all seven drugs that we tested, which are listed up here and resistant to zero. On the other hand, as you get more and more resistant, you go back down here to the bottom right corner, and you'll see these are organisms or isolates to which they are resistant to six drugs and only susceptible to one. So this is a very good pictorial way of telling you how many -- how many drugs to which these isolates are resistant, and, two, where they cluster. By

looking at how dark these dots are clustered, you can see what happens. So I put acinetobacter on here, because that's -- was obviously a topic of discussion for this morning, and you can see that there are two varieties of acinetobacter. One that's susceptible to just about everything, and then the other clustering is down here, which is resistant to five or six drugs and only susceptible to one or two. On the other hand, nobody would argue that Group A streptococci can also cause serious wound infections, necrotizing fasciitis, et cetera. But what you see here is that the vast majority of those are susceptible to just about everything you test, and there's nothing down here that's resistant to five or six of those drugs. So not saying that Group A strep doesn't cause serious and life-threatening disease, but it's susceptible to a lot of the drugs we still have. This is also the difference between nosocomially-acquired MRSA and community-acquired MRSA. When you go back to the history of medicine, the reason why MRSA was such a drastic change, was at the time when penicillin resistance came out, penicillin was the only drug we had. So what happened -- came out second was vancomycin, which was world saving, and then methicillin comes out. So when methicillin resistance occurs, all of a sudden we don't have any drugs to treat staph aureus. That is not the case today for community-acquired MRSA, where the vast majority of these organisms remain susceptible to clyndomicin,

800-497-0277

tetracyclines, (inaudible). Do those drugs work? Does clyndomicin cross-resistance with erythromycin mean anything? That's why we need the clinical trials data to be able to know that information and relate the susceptibilities to clinical outcomes.

Let's go to the next slide.

So when we look at something like acinetobacter, can't we say, "Well, what drugs do we have left when we get out to this point?" So what we've done with the Focus Technologies' data is to be able to drill down and say, "For these six drug-resistant isolates, what is the resistance pattern for these?" And you can see that what's left down here is carbapenems as really the last ditch drug that remains in vitro susceptible for these multi drug-resistant acinetobacters. The other thing we can do is by looking down these columns, we can see which drugs we lose first, which comes second, which comes third, so we can look at the pattern at which we lose these resistance -- lose these drugs.

So what are our future needs, then? What we really need is data on relating clinical outcomes to in vitro resistance, which is so lacking. The question that got asked this morning of how can you do some cost benefit analysis of where the biggest problems are, really then gets back to what is the impact of resistance. Because if resistance doesn't mean anything in terms of clinical outcomes, then why should

that even be a problem? And I'll give you another example. For instance, we know from several clinical studies now that the break point for streptococcus pneumonia for penicillin is wrong. It is set at two as a level of high-level resistance. And yet for pneumonia, we know that up to an MIC of four, those people do just the same as if they had an MIC of .5. Yet for various reasons and discussions with the NCCLS, that break point still remains at two today, even though it doesn't predict clinical outcomes. So what we're telling people when they get the big R next to penicillin when they get a clinical isolate is don't use penicillin, when, in fact, that is untrue for the vast majority of isolates in the United States. So we are trying to work to come up with some unified definitions of what resistance really means and link that to clinical outcomes. Obtaining this patient-level data is often difficult and very expensive. We tried to do it through Focus Technologies and it became prohibitively expensive to go back and find the charts of all those little dots on those grafts, and then to try to actually pick that information out

of the charts is just a monumental task. Existing databases often don't allow us to determine how accurate is the diagnosis. When somebody writes down sinusitis on the page, do they really have bacterial sinusitis or was that just somebody with a cold that got misdiagnosed? We can't judge, then, the appropriateness of antibiotic usage, because we

don't know whether the person really needed the drug or not. We can't tell why they got the antibiotic, and we also can't make accurate assessments of outcomes, because in certain settings like the emergency room, all you know is they got a drug and they left and they didn't come back. Does that mean they got better? Nobody knows.

So the -- how about prevention and control? Well, the FDA and the CDC have undertaken this "Get Smart" program to try to foster appropriate use, which as I said, really creates an area of tension with the pharmaceutical industry because this limits the market. We need data that appropriate use is also associated with positive outcomes. One of the things that I hear all the time is, "Well, by giving antibiotics to all these people, we are preventing these very rare serious complications that may occur with some of these diseases." The existing data, however, does not support that. The antibiotics actually prevent serious outcomes.

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So there's a real and present need for clinical trials in industry -- in areas that industry cannot or will not support. And this problem is really a resource problem. Action Item No. 80 on the public health action plan says that we as federal agencies will perform clinical trials that are not economically advantageous for industry. How we are going

to accomplish that is going to be a big issue. And, again, this seems like a tremendous undertaking for anybody. In looking at Colonel Vaughn's presentation right before mine, the question is, does DoD even have the resources to be able to do any of these trials? The data on the magnitude of the benefit of antimicrobials in these less serious self-resolving diseases really remains unknown. And the reason I put uncomplicated skin infections on here is because when we went down to the CDC about a month ago to talk about community-acquired MRSA, we looked at people that just had cutaneous abscesses. And it appears that no matter what antibiotic they got, that it was really the incision and drainage that was the primary thing that was making the person better. So does this mean we should tell everybody to stop giving out cephalexin and shift over to linezolid just because community-acquired MRSA is out there? Even scarier what we heard at that meeting is people were getting admitted just because they had MRSA. They were fine. They lanced their -- they ID'd the abscess, they were doing fine, but the clinician saw MRSA on a culture report, panicked, and stuck them in the hospital. That's probably the worst place to be if you don't want to get a resistant pathogen. So can we give some better guidance to clinicians out there about this? And, again, that all comes back to how you define resistance and what are the clinical outcomes with it. And how do we get data on the

efficacy of older generic drugs against some of these diseases? Should we really be so careful about clindamycin in community-acquired MRSA? We went back and reviewed all the literature there is and found only two case reports of people who got clindamycin when they had an originally clindamycin-susceptible and erythromycin-resistant MRSA. One of those people had endocarditis. Clindamycin, not my drug of choice for endocarditis. Anyway, and the other one had an empyema. Everybody that had a skin infection with an erythromycin-resistant, clindamycin-susceptible staph aureus got better. And the reason might be because you're eliminating the bugs before they can get induced resistant. And the other issue is, people don't get erythromycin first and clindamycin second, which is what happens in the test tube or on the culture plate. So how do we get data on whether some of these drugs will be effective or not? Since these drugs are generic, there is not a drug sponsor who is interested in looking at those. So, again, the likelihood the industry is going to come up with these -- the money to do these studies is highly unlikely.

So the last thing that I was really glad to hear about is rapid diagnostics will absolutely transform how we prescribe antimicrobials and how we do clinical trials. So first of all, it has clinical practice implications in that it can guide the appropriate use for patients who truly have

bacterial disease if the diagnostic test is capable of determining that. Look at rapid streptococcal testing in the throat of kids. Only 15 percent of those kids actually have Group A strep. So if you can eliminate all the kids that don't need the drugs, that's really very helpful. It will also change the face of drug development. Right now sponsors don't want to develop narrow-spectrum agents because people won't use them. Everybody wants to use a broad-spectrum agent because you're not really sure what organism the patient has. So it will make the drug development of narrow-spectrum drugs much more tentacle. It also has huge implications for clinical trials. Right now you can screen loads of patients trying to find the people with bacterial disease. And it's very, very difficult, as I said earlier, to find the patients with resistant pathogens as well. If you had a test that you could do right off the bat in people -- and there are some of these developing. We're talking about -- we're having an advisory committee meeting in October about developing an indication for primary staph aureus bacteremia in people without a source. And in talking with folks at the NIH and reviewing the literature, we found a fluorescent antibody blood test that you can do right off a blood culture to tell whether somebody has staph aureus or staph epidermidis. Because if you didn't do that, imagine how many staph epidermidis people you would get into the staph aureus trial.

It would overwhelm the number of people with aureus, and you would have to enroll loads and loads and loads of people to find an adequate number of people with staph aureus.

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So, really, where's the big hole here that none of us can really address? It's discovery of new classes of antimicrobials. This is a huge undertaking. It's not like people haven't tried. And for 40 years, we really have had very, very great difficulty in doing this. Alterations in existing classes may still be helpful. We saw in the last year the approval of telithromycin, which was an alteration of a macrolide drug. So -- and the other point I want to make is, that when you hear this, "There's only five out of 506 drugs in development for antimicrobials," that number really only looks at large pharmaceutical companies. The issue is -- we were asked at FDA to help come up with that information, and we can't give it to anybody. We cannot discuss which drugs are under development by which companies because that's considered proprietary information. But I can tell you -- I can list off the top of my head at least five or six drugs that are looking at MRSA related infections that are being developed by smaller biotechnology companies. So that doubles the number right there. Where is the hole? Gram-negative rods. There is hardly anyone developing drugs for gram-negative rods. And I think Colonel Vaughn pointed it

out. If you are going to develop a drug, it takes you ten, 20, 30 years to get to that point where you're going to get to doing Phase III clinical trials. So we need to do something about this today if we're going to have drugs down the line ten, 20 years from now for these gram-negative rods.

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So let me just finish up then and summarize. This issue with drug discovery has existed for 40 years. It's -- the reasons why the large companies are exiting antimicrobial development are really primarily economic. Their money can be spent better elsewhere and get much more back for it. There's this tension between appropriate use and limiting the market, the public health good versus the economic bottom line. And the need for new drugs is really greatest and serious in life-threatening diseases where the market is smallest.

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The need for data on the impact of in vitro resistance with clinical outcomes in various diseases will help us do that cost benefit analysis of where we need to look the greatest. The data on the clinical impact of appropriate use strategies would be very helpful. Clinical trials in self-resolving diseases and data on use of older generic drugs will be exceedingly helpful. Rapid diagnostics would really

help us in terms of both the clinical practice and clinical trials. And the last thing that still hangs out there as a big question mark is, who is going to do the new drug discovery to come up with new agents?

So I'll stop there, and hopefully you'll have some questions for me, if I didn't burn you all out before lunch here.

DR. OSTROFF: Thanks, Dr. Powers, for a terrific presentation. Let me open it up to Board members. First Dr. Cattani.

DR. CATTANI: Yes. Thanks. That was a really thorough and comprehensive presentation. About 50 to 75 percent of it could have been given about malaria 20 years ago. And I think there are just two points that I would like to make. One, on your suggestion of looking at in vivo versus in vitro resistance, this was done at great expense and under great logistical difficulties in the field in malaria in developing countries. And it certainly -- the results showed that in the case of chloroform, for example, yes, you could have in vitro resistance and in vivo sensitivity. The issue is spending a lot of money on those kind of trials gives you a snapshot at one point in time, and the whole resistance process is dynamic. So that if you take chloroform, for example, there was a period when in vivo resistance was much less than in vitro. But shortly after that, chloroform was

like water in most of these areas. So getting results at a certain point in time is not necessarily going to help you with the future.

And the second point I would like to make is the role of Walter Reed and your military in developing antimalarial drugs. There were a lot of drugs listed there, and I don't think people should be left with the impression that Walter Reed actually had the same role in each of these drugs. In some of them, they were a key factor, in methoquin, for example. But in drugs like Malarone, they collaborated very much with the pharmaceutical industry that developed it, and so there wasn't one model. And perhaps one of the things that should be discussed later on is, how can this -- the role that the military played in drug development and that relationship with either the pharmaceutical companies or the universities or whatever -- how can that be somehow codified and -- because the road forward doesn't seem to be strictly with the pharmaceutical companies nor strictly with the military, since there isn't enough money. So...

DR. OSTROFF: Comment, Dr. Powers?

DR. POWERS: Yeah. I've often asked myself the question, why does this work so well in malaria and not in other drug areas? I think -- let me comment on the resistance piece first. I think malaria is a serious and life-threatening disease. It can kill you. And I think that

there's a lot -- it's a lot easier to show resistance in that setting. I think what we're worried about is diseases. And so what we want to say -- what you're saying is the relative proportions of people who fail with resistance may differ as resistance expands.

That's not the question we're asking. The main question we're asking is, does resistance mean anything, period? So, for instance, let's take macrolide resistance in streptococcus pneumonia. You can say, well, we put it into a test tube and it looks like it's resisting. Well, it's resistant because you drew this line where the break point is. And where did that number come from? It comes from the blood level of the macrolide. Well, that means absolutely nothing. Because we know that epithelial lining fluid concentrations of macrolides, which is where the infection is in pneumonia, are astronomically higher. So it's not a surprise, then, when you say, "Well, we looked at the telithromycin database and all the people that got clarithromycin, for clarithromycin bacteremic strep (inaudible) pneumonia, they all got better." So that -- that really starts to make us ask that question. I think cloroquin and malaria is a different issue in terms of -- you know, it's a serious and life-threatening disease. And as long as we know that the pharmacokinetics of the drug are not what's impacting outcomes, that's a little different. So I think there is a little different issue.

And, again, the piece of how can we codify what -- how we develop malaria drugs and expand that, I would love to know that. That's something I hope to learn today, is how we can -- how we can work together to do that.

DR. OSTROFF: Dr. Gray.

DR. GRAY: Dr. Powers, that was an excellent presentation. I just -- we've been asked basically to wrestle with the question, is the DoD appropriate to pursue, as you say, new platforms? And let's assume for a minute that the decision was made to do that and funding and the technical expertise are there. My question is, is the DoD's approach to malaria appropriate for the new platform discoveries and other antimicrobials, such as antibacterial agents? And I wondered if you could comment on what strategies, whether they be complementary alternative medicine approach or engineering strategies, have been successful in identifying new platforms. I think the DoD strategy was screening thousands of known compounds, not engineering new compounds and not searching for them in nature. So I'm wondering what works today.

DR. POWERS: That's the problem. In the antibacterial realm, nothing has worked. People have tried genomics in terms of developing new drugs. And what's fallen down there is, there are any number of -- literally thousands of targets within the bacterial cell that you can try to attack. So people do these high screenings where they try to

find the target. Then they try to do it in a whole bacterial cell. It doesn't work, because the biggest barrier to this is the cell wall. None of these potential compounds get through the cell wall, especially in gram negatives, to be able to attack where they need to get to. So the screening methods perhaps need to be a little different in terms of viewing wholesale (inaudible) as the screen rather than doing just wholesale throughputs.

The question is, how can DoD develop new drugs like -- and I'm not familiar enough with the malaria piece, and that's what I wanted to learn today. And I was not clear that the DoD actually, you know, invented those things. They -- like you said, the screen natural compounds. A number of the large pharmaceutical companies have tried this idea of screening natural compounds. I mean, cephalosporins were discovered in sewer water. I mean, they just fortuitously stumbled across them. People haven't been successful doing that. So, I mean, this is just my opinion, if you ask me this. I don't know how we're going to come up with some of these new drugs. Because the NIH had a drug summit about three weeks ago, and one of the members of the pharmaceutical company that I know pretty well came up to me and said, "It's not like we're not trying to find these things. It has been very, very difficult to be able to come up with these." And let's take the quinolones, for example. The quinolones were

all synthetic modifications of the basic quinolone structure. And what they've noticed is that, yeah, we can get in vitro activity that's off the scale compared to what we have currently, but then those drugs were all associated with significant toxicities. So how can we balance those two things out?

And in terms of -- getting back to your question of how could DoD do this? I don't know. Is it worth -- is it worth repeating the -- what drug companies have already done? That would not seem to be a great use of resources. So I don't know the answer to your question, what the best way is to do this, because the large pharmaceutical companies with all their resources have really had a tough time doing this.

DR. OSTROFF: Grace.

DR. LEMASTERS: I was just looking at your Slide No. 14 where you say, "Clinical correlation of in vitro resistance with clinical outcomes," as a key issue that the FDA would like addressed. And I was just thinking of a somewhat straightforward way that could be addressed is with the use of the VA hospitals. If there could be a coordinated effort, and congressional, with the funds support of this surveillance, it's like -- it's like the ideal system. When I mentioned before about there's a train going down the track, I am talking about also the baby boomer cohort that is aging

quickly as we look around the table here, and there's going to be a susceptible -- a huge susceptible population as -- of the aging cohort. So it seems like we're sort of prime to start looking at that question in a coordinated fashion at least among like our veteran hospitals.

DR. POWERS: It would be nice to -- I know, I used to work at the VA before I went into the FDA, and I know that at the time, six years ago, they were computerizing everything in terms of the clinical data from patients. It would be great to work with the VA to actually be able to come up with this information.

UNIDENTIFIED SPEAKER: Well, as the VA representative here, I would say we've come a long way at the VA in the six years, and we now -- all our patient records are computerized, and we do have an office of research and development within (inaudible) that could conceivably take on -- that uses that type of simply administrative data to their health data to do research on it, and we could do such a study. And somebody would have to propose it.

DR. OSTROFF: Okay. Let me just --

UNIDENTIFIED SPEAKER: I have one other --

DR. OSTROFF: Go ahead.

UNIDENTIFIED SPEAKER: -- just one other question. It was essentially about -- it seems -- wrestled with some of the many ideas that we were presenting here

today. And it seems like you made a very good case that the clinical significant -- I think as I understood you, the clinical significance of those early resistance in vitro is unclear. There's some uncertainty about what clinically this really means. But then you call for the development of new drugs, new antibacterial agents. And it's not clear, if you don't -- it's not clear what the (inaudible) significance is --

DR. POWERS: Let me explain that.

UNIDENTIFIED SPEAKER: -- and the (inaudible) extend that, who should -- who should -- if the pharmaceutical companies are not going to see this as profitable, I think you also made a very convincing case, then shouldn't the obvious agency to step in, at least in principle, be the NIH?

DR. POWERS: I'm glad you asked that question, too. Well, let me answer the first one. We don't have any doubt that in serious and life-threatening diseases that resistance can cause a problem. What we're asking for is, what's the proper definition of resistance for a particular organism? That's what we're -- you're going to get to some point where people are going to die related to this. So the question is, what's that level? So clearly at some point macrolide resistance is going to be -- and strep pneumonia is going to become significant, but is it at eight where it's set now, or is it up here at 64? That's what we're really asking.

There's no way we think that resistance at some point isn't going to cause a problem. The question is, where do we draw that line in the sand?

Let me give you an example of where we've had issues with this. A number of drug sponsors have come in to us and asked us for indications like acute bacterial sinusitis due to macrolide-resistant streptococcus pneumonia. Now, why do you think they want that, because nobody else has it. It's all about getting a competitive advantage. And what I've said enumerable times is, these are relative superiority claims. You do a trial that shows your drug is equal to amoxicillin in sinusitis but then say, "But we're really better because we have activity in the test tube against macrolide-resistant strep pneumonia." Well, I would say, "I don't" -- "does it matter what" -- "do we need another drug for sinusitis?" We have 14 drugs approved with acute bacterial sinusitis. But that's where the money is. So what we said is -- and I think in some way what we're trying to do is guide sponsors in a way of saying, "Look, guys, let's get away from these and go to some place where the resistance really matters." And this is the only incentive we have, right, to have say, "We're not going to give away resistance claims for acute bacterial sinusitis, because we don't know what it means. So why don't you go spend your money over here in hospital-acquired resistant acinetobacter." When somebody says, "No, we don't

want to do that," we, at the FDA, can't force anybody to do that. So we're trying to put incentives into the system to push people in that direction.

Shouldn't NIH do it? Where are they going to get the money from? So a third of the NIH budget is for bioterrorism, a third of it is for HIV, and a third of it's for everything else. And this is one slice of the everything else. The other thing is, when I talk with them -- and they're in a tough spot, too. They're working on their 2005 budget today, and the money that's already in it is already allocated to other investigators. So what they've said to me rightfully so is, "If we're going to do this trial that's going to cost $40 million, that's essentially our entire budget," much like the DoD's, "and who are we going to take it away from? That leaves somebody else, you know, in the lurch, too." A very good question, you know, of how are we going to do those things. So I think it's a resource issue for all of us, you know, all of these agencies.

DR. OSTROFF: Well, for those of who probably think that we should have NIH's budget problems --

DR. POWERS: I wish. Yeah, it's kind of hard for me to be sympathetic when they tell me that.

DR. OSTROFF: We're going to have to bring this session to a close. I really appreciate your input in the discussion. Listening to this -- these presentations, let me

make just a couple of thoughts and observations on my part.

When we talk about sort of the 800-pound guerilla in the room, I would say that the pharmaceutical industry in this particular area is probably the 1800-pound guerilla that's in the room. And I just don't see the DoD all of a sudden waltzing into this particular arena with an opportunity to really have a major program and investment with everything that goes on in the private industry side. I think probably the -- the better strategy is to look for some of the niches in the area of antimicrobial resistance that aren't necessarily being filled, particularly in some of these discussions about looking at bolder antimicrobial agents. And when you see a presentation that, you know, colistin is being used, it strikes you that there's probably a lot of arrows in our quiver that certainly the pharmaceutical industry is never going to look at in terms of their utility for some of these infections. And that might be sort of a marvelous opportunity that both DoD and possibly the VA could step in and take a look at.

The other point that I think is somewhat overlooked was something that was mentioned by Colonel Vaughn, which is that the emphasis has always been on prevention measures. And certainly -- and I don't know to what degree FDA is trying to encourage this -- certainly thinking about the potential for preventative modes, particularly vaccines,

for some of these really vexing antimicrobial-resistant circumstances, in my mind, is a far more productive way to invest resources in thinking about trying to continue to make new antibiotics.

And I'm wondering, you know, if you have any parting thoughts about some of those issues?

DR. POWERS: Yeah. I mean, certainly -- and, you know, the issues with the vaccines fall right into this economic area, because getting -- talk about getting rid of your market, right? If you make the disease disappear, that's great from a public health point of view but bad if you're selling drugs to treat that. So that's why the incentives have worked so well for vaccine development in terms of -- not only that, but the indemnification issues that have helped industry. That would be very useful.

Let me just sort of temper that enthusiasm in a way, in that prevention trials are in some ways harder to do. They are easy to enroll people because you take completely asymptomatic folks. But depending upon what the level of infection is, to actually demonstrate a difference between that preventive measure and placebo -- for instance, if you had to demonstrate that you had 2 percent infections in the placebo versus 1 percent, that takes, like, 1,500 patients to do. So those trials need to be fairly large. But they're worth it, because if you can show that there's an effective,

preventive intervention, that -- that really would be very useful. You know, an ounce of prevention, a pound of cure.

DR. OSTROFF: Staph aureus is the best example, probably.

DR. POWERS: Well, let me just say, as an example, and this came up at the meeting down -- that the CDC had in Atlanta. What we have is drug sponsors that want to look at the end points for those trials, "Well, we just eliminated colonization." And let me put a big warning flag out for that. That sounds very logical, and it doesn't work. We've had several drug companies come in who have looked at staph aureus decolonization, and we look at the infection rates, they are identical to placebo. So the problem is sticking something up your nose doesn't get rid of staph aureus (inaudible) from your groin and every place else. So some of these prevention strategies really need to be proven in terms of the end points need to be the actual incidents of infection, not just the ability to decolonize some particular body site.

DR. OSTROFF: Thanks very much. On that note, I think everybody would want to probably wash their hands before we go off to lunch. And I'm going to turn it over to Colonel Gibson for instructions about lunch.

(MEETING ADJOURNED)

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